VOLUME 5
(Old Series, Vol. X)

MAY, 1932

NUMBER 11

ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

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Issued Monthly

ANN ARBOR, MICHIGAN

Rheumatic Heart Disease

A REVIEW*

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THE large volume of literature which has appeared in recent years relating to various phases of rheumatic fever and rheumatic heart disease seemed to require some correlation. An attempt at this resulted in the following review.

While the earliest description of rheumatic fever appeared prior to the middle of the seventeenth century, and the best of these in 1676 by Sydenham, it was not until more than a century later, in 1788, that a clear description of rheumatic heart disease was published by David Pitcairn of St. Bartholomew's in London. Prior to this, Störck and others had noted changes in the thoracic viscera in cases of rheumatism coming to autopsy.

Dillon,[62] in 1850, and Gramshaw,[63] in 1853, used the term 'Rheumatic Carditis' in the titles of published articles. Stokes,[1] in 1853, frequently used this term. He observed that "disturbance of the heart's action, even though without any physical sign of inflammation, when arising in the course of rheumatic fever, is to be considered as showing the proclivity to, if not the existence of, carditis" (page 523); and that "rheumatic fever does not necessarily coexist with arthritis" (page 46). He also made the valuable observation—ofttimes forgotten in these later days—that the cardiac involvement may precede that of the joints (page 47).

INCIDENCE

A recent editorial appearing in Colorado Medicine raises the question of the value of conclusions drawn from mortality statistics in heart disease. While the inaccuracy of individual death certificates is evident, this basis of study remains at the present day the principal source of information as to the incidence and hence of the importance of any group of diseases. Therefore at the outset, reference must be made to mortality and, so far as obtainable, to morbidity statistics. During the past fifty years the deaths from tuberculosis declined 44 per cent, while the deaths from heart disease increased 42 per cent, and during the past twenty-five years in the United States Registration Area the deaths from heart disease outnumber those from tuberculosis. At the present time heart disease ranks as the leading cause of death. The local importance of heart disease is stressed by Washburn[2] who wrote, "In Denver, deaths from tuberculosis fell from nearly 700 in 1917 to 459 in 1927, while heart deaths increased from 157

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in 1917 to 449 in 1927." The same author stated, "If we attempt to classify the deaths at all ages according to etiology we can estimate that approximately 30 to 35 per cent of the whole number are due to rheumatic heart disease."

Heart disease may be divided into three age groups and these in general represent etiological groups. Up to the age of forty the great majority of cases of heart disease are rheumatic in origin. Twenty-five per cent of all cardiac deaths fall in this period.[3] Of five hundred children observed by Wilson[4] and her associates in a heart clinic, 12 per cent died and 88 per cent of the deaths were due to rheumatic heart disease. In New York City[3] heart disease was found to be the leading cause of death among school girls. Among school boys it ranks second only to accidental death. The same records show that heart disease stands second as cause of death in young adults ranging in age from fifteen to nineteen years.

The second age period in heart disease is from forty to sixty years, when syphilis is the most important cause of death. The third period extends from sixty years on, when cardiac deaths are chiefly due to degenerative changes.

It is unfortunate that we have no satisfactory morbidity statistics, since heart disease and rheumatic fever are not reportable diseases, but Emerson[5] estimated that for every death from heart disease there are probably seventeen people suffering from heart disease, while there are only seven cases of tuberculosis for every death. Dublin[3] was more conservative, estimating ten cases for every death from heart disease, and stating that at ten years of age an individual is three times as likely to die from heart disease as from tuberculosis.

Deductions drawn from the incidence of rheumatic fever are of doubtful value since the conception of what constitutes rheumatic fever is and has been rapidly changing in the past decade. Practically all figures obtainable relate to frank cases of rheumatic polyarthritis and disregard those cases presenting the nonarthritic manifestations of this disease.

During the war about 5 per cent of the men in the draft were excluded because of organic heart disease. Combined school, industrial and insurance statistics show that from 2 to 2.5 per cent of the population have some form of organic heart disease. Emerson[5] stated that not less than 1 per cent of the population requires care for some class of heart disease. It is thus evident that as an economic load heart disease at least equals in importance that of tuberculosis.

Autopsy Statistics. Cabot[6] presents statistics from 4,000 autopsies (a total of 4143 cardiovascular lesions in 1906 persons) which show that rheumatic valvular heart disease is twice as common as syphilitic aortitis and five times as common as syphilitic valvular disease. Mitral stenosis, alone or combined, is three times as common as all other rheumatic valve lesions combined. Mitral stenosis uncomplicated is two times as common as any other single valve lesion. Figures show a falling off in the amount of fatal rheumatic heart disease but show no falling off in the amount of pericarditis. The age at the time of death is most often thirty to thirty-nine years.

The incidence of family infection in rheumatic fever is about that of tuberculosis. St. Lawrence[7] showed that in 50 per cent of families two or more persons had rheumatic infection. Faulkner and White[9] gave 35.5 per cent as a comparable figure. Swift[8] stressed the house and person to person infection. While there is usually a low grade of contagiousness this disease may assume epidemic proportions.[11,12] It appears probable that the lungs serve either as a portal of entry for rheumatic infection or as a source of reactivation. Numerous authors have called attention to the relationship at times observed between bronchopneumonia and rheumatic carditis.

Associated Conditions

Coburn[13] in an excellent monograph considers the relationship existing between rheumatic fever and upper respiratory tract infections, both in the initial and recurring attacks. Having noted that rheumatic fever is extremely uncommon in the tropics, he transported ten patients with active rheumatic fever from New York to Porto Rico for a period of six months, so far as possible avoiding any change in the management of these patients other than that of climate. In brief, his results showed that the rheumatic process, severe in New York, subsided during three months in the Tropics, disappeared clinically during six months in the Tropics, and evidenced itself with sudden reappearance of symptoms in some instances shortly after the return of these patients to New York. These observations strongly suggest that the rheumatic state was influenced by the change in environment.

Nichol,[14] in a study of the incidence in Florida of two common diseases encountered in the colder states of this country, namely, rheumatic fever and pneumonia, notes an extremely low incidence of rheumatic fever, whereas that of pneumonia is relatively much higher: "Among 31,000 hospital records there were 10 cases of rheumatic fever or chorea and 152 cases of lobar pneumonia." He believes that we should find among children born and reared in this area practically no heart disease of rheumatic origin.

The weight of evidence seems to indicate that rheumatic fever is most frequently encountered in the temperate countries, but Paul[15] furnishes some interesting exceptions to this rule. For details as to the theories and known facts relating to the geographical distribution and of family and environmental influences associated with rheumatic fever the reader is referred to his recent report.

Rheumatic fever is especially invasive in early to middle childhood and at this age period when its onset is especially insidious, the visceral phenomena (carditis, etc.) are more frequently observed than at a later period when arthritic phenomena predominate. Puberty appears to be a critical period, but following this the tendency to rheumatic infection diminishes. Girls appear to be definitely more susceptible to rheumatic carditis. In addition to rheumatic fever, chorea, tonsillitis and other types of streptococcal infection of the respiratory tract, scarlet fever and puerperal sepsis have been considered to bear an etiological relationship. Swift[16] especially stresses the importance of streptococcal focal infections (tonsillitis,

sore throat, pyorrhea and apical abscesses) as predisposing factors in rheumatic fever and rheumatic heart disease. It must be admitted, however, that in the majority of cases of focal infection this relationship is assumed rather than proved.

Newsholme, in England, showed the greatest number of cases to occur in those years in which the annual rainfall is lowest, while in the United States the disease is most prevalent in the spring months. Against the theory of dampness being a factor is the fact that during the war in France rheumatic fever was noted to be comparatively rare in spite of the exposure in trench life.

Because of the intimate relationship which exists between rheumatic fever and chorea, it is generally assumed, though by no means proven, that the infectious agent is identical. Riesman and Small[17] include chorea as a manifestation of rheumatic fever. The incidence of the appearance of rheumatism antecedent to chorea varies according to different authors from 9 to 71.5 per cent. In Oxford Medicine[18] appear the following figures on the incidence of rheumatism antecedent to chorea:

Apt and Levinson	143 cases	9 per cent
Branson	67 cases	71.5 per cent
Collective Investigation Committee of B.M.A.	439 cases	26 per cent
Osler	554 cases	15.8 per cent had acute or subacute joint swelling either preceding or subsequent to chorea

While these figures appear contradictory, it must be borne in mind that there is often great difficulty in determining the presence of fleeting articular involvement, that vague joint and muscle pains are not always susceptible of exact classification and that the rheumatic infection may not become manifest until after the chorea has passed away. Nodules occurring in the vicinity of joints in chorea are, according to Kaufmann,[19] analogous to Aschoff bodies and hence furnish further evidence of the etiological unity of these two diseases.

It seems desirable to stress this relationship of chorea and rheumatic heart disease since not all pediatricians appear to recognize it. Waggoner[20] in a recent article on chorea barely mentions this relationship and in his consideration of treatment makes no mention of the prevention of heart disease in chorea or of the care of the choreic cardiac patient. In the present state of our knowledge it is wise to search diligently for a history of frank or masked chorea in childhood in connection with the obtaining of the history of any cardiac patient.

Bacteriology

No attempt will be made to review all of the literature relating to this phase of the subject. There appears, however, to be a unanimity of opinion that some form of streptococcus, or perhaps many forms are capable of producing rheumatic fever and its sequel, rheumatic heart disease. The work of Small[21,22] and his associates has attracted considerable attention in recent years, although this work has not been substantiated by other work-

ers. He presented the *Streptococcus cardioarthritides*, which possesses a specific immunity identity. Isolated first from the blood of the rheumatic fever patient, then from the throat, it is claimed that it is capable of producing characteristic arthritic and cardiac pathology in rabbits, including Aschoff nodules, and that a specific serum can be prepared with it.

The organism is a spherical Gram-positive coccus which in fluid medium yields diffuse growth and shows short chain formations. It is readily stained by the ordinary aniline dyes. It is nonmotile, aerobic and facultatively anaerobic. Neither flagella, spores, nor capsules are demonstrable. It is of rather constant, uniform size, varying from 0.7μ to 1.2μ in diameter. The optimum temperature for growth is 37° C., but growth at low temperatures occurs. Regarding sources of *Streptococcus cardioarthritides*, Small in his recent report mentioned only the throat and blood and evidently doubted his former finding from feces. He stated that the organism is found regularly in throat culture in cases of rheumatic fever or chorea and has been obtained in three instances from blood in rheumatic fever. Cultures should not be made from the crypts of intact tonsils, since these usually show *Streptococcus viridans, hemolyticus*, etc., but from the superficial sites in the pharynx—pillars, uvula and soft palate.

That other organisms than *Streptococcus cardioarthritides* may be the cause of rheumatic fever and the usual manifestations of rheumatic heart disease was shown by Tredway,[23] who reported the case of a boy of 13½ years who had had two previous attacks of rheumatic fever with carditis. In the third attack there was a mild pharyngeal infection with a septic temperature running to 103°. The blood culture showed *Streptococcus viridans* on three occasions. Later there was pericarditis and effusion. Rheumatic nodules were noted at the end of the twelfth week and were present only on the scalp. There were no petechiae or other evidences of emboli. The only joint involvement was in the left metacarpals and left shoulder for but four days. The reasons given for reporting were the unusual blood findings, the absence of joint symptoms, except as above, and pericarditis with effusion. Small[24] pointed out that from the clinical standpoint confusion has arisen in the differentiation of rheumatic endocarditis and bacterial endocarditis, particularly in the transition stages of the former into the latter. A streptococcus obtained in the blood culture of a patient might arise from either the one or the other of these conditions.

Clawson[25] tabulated the bacteriological results of blood, joint and pericardial exudate cultures as reported by various workers and states, "The conclusion to be drawn from the findings of the various workers on the basis of morphologic, cultural and immunological characteristics is that the group of streptococci isolated from cases of rheumatic fever cannot be considered a specific one, but that it represents a heterogeneous group, generally green-producers on blood agar, with moderately low virulence."

Cecil,[26] et al., found a streptococcus —usually *viridans* in type—in the blood and joints of a high percentage of rheumatic fever patients. They

noted, however, that indifferent or even hemolytic streptococci may occur.

In addition to our lack of accurate knowledge as to the causative organism, we are likewise uncertain as to whether there is direct bacterial invasion in all cases, or whether there is simply a local tissue reaction, allergic in nature, to toxins produced at some distant bacterial focus. Comparative studies of rheumatic fever, tuberculosis and syphilis suggest that in the former, as well as in tuberculosis and syphilis, there is an allergic factor. Swift[27] demonstrated that the intradermal injection of living streptococci into rabbits produced not only an immediate inflammatory reaction, but in addition a later but milder inflammatory reaction, which occurred in the absence of living streptococci in the involved tissues. He also showed hypersensitivity of the skin of rheumatic fever patients to streptococci, which he interpreted as a specific allergic manifestation. Kinsella[28] has cited another example of allergy which apparently occurs in gonorrheal rheumatism. He pointed out that gonorrheal arthritis never occurs in the early state of the urethritis but after several weeks or months and then apparently associated with some other condition which permits a blood invasion. Then we have a totally different response on the part of the body to bacterial invasion.

Pathology

Limitation of space prevents any extensive consideration of pathological changes, but it should be stressed that rheumatic carditis is usually a pancarditis, that while the acute involvement of the pericardium and myocardium is usually transient and clears with little or no permanent impairment of these tissues, that of the endocardium usually leads to deformity with resultant hindrance to the filling and emptying of the heart chambers—a condition which secondarily leads to muscle damage.

Lasèque[29] wrote, "Rheumatism licks the joints, the pleura and meninges but bites the heart."

No attempt will be made to present a systematic description of the pathological changes in rheumatic heart disease, but in the course of this review certain investigations and ideas presented by the various authors were sufficiently striking to merit comment. Reid[30] classified pathological lesions in rheumatic fever as exudative and proliferative; the former changes are found in the joint and serous cavity involvement, the latter in the endocardial and myocardial changes and in the subcutaneous nodules which so frequently accompany this disease.

The two working theories as to the cause of valvulitis are: (1) That trauma of contact of the valve cusps at the line of closure resulted in the lodgment of organisms at this point with subsequent formation of vegetations; (2) That bacteria in the blood stream lodge as emboli in normal capillaries which occur in the valve leaflets. Kerr[31] on an experimental basis concludes that both of these factors are operative in the production of valvulitis.

Opposed to the usual opinion Crummer[32] stated that mitral insufficiency (organic) is one of the least frequent valve defects. But Kaufmann[19] wrote, "Mitral lesions, chiefly insufficiency, constitute two-thirds of all valvular

lesions." These figures are drawn from autopsy findings. Another interesting note regarding rheumatic valvulitis is that of Cabot,[33] who stated that he had never seen a proven case of tricuspid valvulitis, although Libman[34] and Thayer[35] have shown its occurrence in 44 and 66 per cent of their cases respectively.

The infrequency of early right sided lesions may be due to the fact that in early life the blood supply to the right heart is comparatively better than to the left.

The most commonly mentioned myocardial lesion is that described by Aschoff—the Aschoff nodule, a submiliary collection of large spindle-shaped or branching cells containing large, at times multiple, nuclei. These giant cells, usually grouped in a radiating or fan-like arrangement and occurring in the interstitial tissues, are subendocardial and usually perivascular. While this is mainly a proliferative reaction, there may be associated a varying number of polymorphonuclear leucocytes, lymphocytes, eosinophiles and plasma cells. The centers of these nodules undergo necrosis and may later become completely fibrosed. When these occur in the interventricular septum there may be serious involvement of the conduction system with varying degrees of block resulting. Aschoff and others considered these to be pathognomonic of rheumatic myocarditis; but in the past decade groups of giant cells, which could not be readily differentiated from the Aschoff body, have been occasionally demonstrated in other conditions, in general in infections due to streptococci of low virulence. It is thus apparent that while in rheumatic carditis there is a tissue reaction which is usually characteristic of the disease, the finding of these bodies—in the absence of other evidence—must not be accepted as proof of the existence of rheumatic myocarditis.

Von Glahn[36] feels that changes in the left auricular endocardium, previously described by McCallum, are as distinctive and characteristic as the Aschoff bodies. These changes consist of irregular furrows and ridges on the endocardium which terminate at the line of closure of the mitral valve leaflet. In these are found polymorphonuclear leucocytes, small and large mononuclears and wandering cells—a cell group with none of the characteristics of the Aschoff bodies.

As an explanation of the absence of mitral stenosis in advancing rheumatic carditis Smith and Sutton[3] stated, "Fibrosis of the mitral valve does not always cause narrowing of the channel because the walls of the ventricle become weakened by the lesions in the musculature, so that the ventricle and the auriculoventricular rings become stretched. In spite of the cicatrization, the mitral channel is thus often held open, making the opening larger than normal and allowing regurgitation." Later in discussing mitral insufficiency they state that the early mitral insufficiency is due less to the condition of the valves than to the myocardial factor which causes muscular relaxation, permitting stretching of the rings.

The earlier descriptions stressed the importance of valvular lesions and of the Aschoff nodule as an evidence of the myocardial lesion; but other studies, notably those of Klotz,[37] have shown that certain portions of the

arterial system are as frequently attacked in rheumatism as is the musculature of the heart. Klotz, Allbutt,[38] Von Glahn[36] and others stressed the importance of aortitis, aneurism, pulmonary artery lesions similar to those in the aorta, and peripheral vascular lesions in rheumatic fever. Discussing aortitis, syphilitic and rheumatic, Klotz noted, "In syphilis the disease rarely comes to a standstill, at least in so far as the recognized and studied cases indicate." In rheumatic disease of the aorta the process usually comes to an end spontaneously, but always predisposes the involved areas to recurrent attacks. Regarding the frequency of aortitis in rheumatic fever he stated, "The almost constant presence of some inflammatory reaction in the ascending limb of the aorta should be recognized as an associated condition in this disease."

Allbutt[38] stated that rheumatic aortitis is not rare but usually unrecognized; being usually superficial, it is often painless and in most cases it arouses no symptoms. Numerous other authors have cited cases of aortitis and aneurism in children, of rheumatic origin and often associated with typical anginal symptoms.

Myocarditis may occur in the absence of demonstrable valvulitis. Cabot[39] reported the case of a boy of fifteen who had a fibrous rheumatic myocarditis, particularly of the left auricular wall. There was no acute endocarditis but fibrous thickening of the mitral and tricuspid valves without stenosis or noteworthy insufficiency. Dr. T. B. Mallory stated that this was the second case seen in four months—a pure rheumatic myocarditis.

Mackenzie,[40] in discussing pericarditis, stated that when pain is present it will be found invariably that there is evidence of myocardial affection. Swift[8] stressed the fact that pericarditis is not of itself painful. Regarding the frequency of myocardial involvement there are varying opinions. Aschoff bodies, the accepted pathological evidence of myocardial involvement, are demonstrated frequently at autopsy, but whether they frequently or always occur with the first attack is a question which has caused considerable controversy. Allbutt[21] wrote that the myocardium is probably involved in every case—the endocardium and then pericardium coming next in order. The first symptom is usually palpitation and stabbing pain over the heart or a feeling of tightness or oppression in the left breast.

Coronary changes have not been considered of importance in rheumatic heart disease until very recently. Perry,[41] in 1930, reported eight autopsies upon cases of rheumatic fever carditis showing coronary changes. This study was incited by the findings at the autopsy of a child who during life suffered from typical anginal pain in the course of a severe rheumatic carditis. The main branches of the coronary arteries showed severe intimal thickening, with a considerable reduction in size.

Any discussion of coronary and myocardial changes in rheumatic fever and rheumatic heart disease would be incomplete without a reference to the electrocardiographic evidence of these changes. Peel,[42] Wyckoff,[43] et al., have noted changes in the T wave and in the conduction time. Wyckoff and his associates noted wide and inconstant variations in the A-V conduction

time and that there is no proof that they are influenced by salicylate therapy.

Master[44] reported the frequent finding of flat T waves in one or more leads and noted that in subsequent observations these waves may become inverted, or if taken at a later period may again become upright, indicating in either case a progressive myocardial change. Slater,[45] in a recent report, presented three cases which showed inversion of the T waves occurring in the course of rheumatic fever. These were all in adults, suggesting a greater arterial vulnerability. This author believed that this represents a coronary occlusion, not necessarily due to thrombosis, "but that the specific lesion in the vessel may be the site of considerable edema, as in any exudative condition, and that this may account for the closure."

Certain authors[43] have attempted to formulate diagnostic criteria based upon the type and degree of T wave changes. A review of the material in the Colorado General Hospital and of cases seen in private practice fails to substantiate these claims. For the present it would seem preferable to depend upon evidence of arrhythmias, of conduction disturbances between the auricles and ventricles or within the ventricles, and abnormal preponderance of one side of the heart. Not infrequently the electrocardiogram will furnish the only sign of cardiac involvement—in fact, cases have been reported in which these changes have occurred before any other evidence of rheumatic infection had become manifest.

Pericarditis. Cabot[6] stated that the pericardium in childhood is more sensitive than in later life, hence pericarditis is more frequently encountered at this period. Allbutt,[46] writing in Oxford Medicine, stated that the incidence of pericarditis in rheumatic fever is about 10 per cent. He had the impression that pericarditis is less frequent in rheumatic fever than a generation ago and suggested that salicylates may have more of a protective influence in pericarditis than in endocarditis. Pericarditis may precede any grade of arthritis in the young; in older cases it is found only in the severer forms. Combs[3] stated that 53 per cent of all cases of all ages show pericardial changes at autopsy—though not clinically. Rheumatic pericarditis is never suppurative. Regarding pericardial effusions, Mackenzie[40] has never found any serious embarrassment of the heart from even extensive effusions!

The question as to the frequency of carditis in rheumatic fever has attracted considerable attention. Swift[8] stated, "The infection in childhood leads more frequently to cardiac sequelae; indeed it is often questionable whether the first tissue to be attacked by the virus in the early years of life is not that of the heart." In a series of eighty-one rheumatic fever patients[47] he obtained electrocardiographic evidence of functional cardiac disturbance in over 90 per cent. Wilson,[4] et. al., stated, "The heart is probably always effected at the onset of this [rheumatic fever] disease." White[10] stated, "The rheumatic infection usually or always involves the heart."

All recognize the tendency of mitral stenosis to remain "silent" throughout many years after the acute rheumatic attack. Yet there must in many cases

be some progress during this interval. Riesman and Small[17] conclude that the cardiac involvement is part and parcel of the rheumatic process and is no more a complication or a sequela than is involvement of the shoulder joint a day or two after that of the knee joint. Certain other authors state that they have never seen a child below ten years of age suffer from rheumatic fever without involvement of the heart. Mackie[48] analyzing 366 cases of rheumatic fever found that at five years of age 61.5 per cent, and at ten years 78 per cent, presented evidence of carditis in the first attack. Washburn[2] in a recent paper read before the Denver County Medical Society stated that he was certain carditis did not always occur, that he had followed a considerable number of children in which there was never any evidence of carditis. Certainly the failure to demonstrate carditis during an attack is insufficient proof of an intact heart since the murmurs of endocarditis may only be demonstrated months after an attack.

Von Glahn[36] presented some interesting figures relative to the possible duration of active rheumatic carditis. In his series of 109 cases he noted that 35 of the cases had a free interval from arthritis of one to thirty-eight years, yet had acute rheumatic disease at the time of death; and that in 50 per cent of those with arthritis, acute rheumatic cardiac lesions may be found when there has been freedom from joint attacks for intervals as long as thirty-eight years. In other words, there is either reinfection without joint symptoms, or persistence of the infection in masked or latent form—often over many years.

With each decade of life there is less liability of permanent cardiac damage in rheumatic fever, which means that for the prevention of rheumatic heart disease the early attacks of rheumatic fever must be prevented. Typical acute rheumatic fever is rare after forty, for at this period of life polyarthritis is apt to be preceded by a "cold" or influenza, and the cardiac picture is quite different from that associated with childhood rheumatism.

As a means of prevention of rheumatic fever in childhood, tonsillectomies have been extensively performed on the theory that the tonsils represent the primary site. Certain it is that the incidence of rheumatic fever is greatest in the young where there is an excess of lymphoid tissue. Swift's series shows that tonsillitis is an antecedent of rheumatic fever in about 50 per cent of cases. Kaiser,[49] in a study of 439 rheumatic fever children, found that nearly twice as many children developed the first attack of rheumatism when the tonsils had not been removed and that after tonsillectomy recurrent attacks occurred 10 per cent less frequently; but in general the results of tonsillectomy have been disappointing in the prevention of rheumatic carditis. A tonsil stump may retain sufficient infection to cause a recurrence or an initial rheumatic infection. Riesman and Small[17] obtained cultures of *Streptococcus cardioarthritides* from the "superficial sites in the pharynx" and suggested that surgical removal of the tonsils will not eradicate these foci. Katz[50] described these foci as "postoperative foci". It is probable that the tonsils are only one of the portals of entry and that any infection of the up-

per respiratory tract may prove equally responsible.

At the present time we have no certain method for the prevention of rheumatic infection in childhood, but much can be accomplished toward the prevention of cardiac sequelae if the earliest manifestations of rheumatic carditis are recognized. Childhood rheumatic carditis may occur in a mild form with symptoms only of undue fatigue, pallor, loss of weight and appetite, or failure to grow and gain in weight, and only slight dyspnea on exertion. On examination, aside from moderate anemia and undernutrition, with slight increase in pulse rate, there may be no demonstrable signs. These cases present a striking similarity to tuberculosis. In connection with the milder symptoms the frequency of effort syndrome at puberty should be recalled.

When rheumatic fever is denied, search for a history of chorea, frequent tonsillitis, fleeting growing pains and purpura. The frequency and severity of infantile and adolescent pneumonia, pleurisy and painful conditions of the chest may be evidence of earliest heart disease.

Clinical Picture

In any discussion of the clinical picture of rheumatic heart disease it is necessary to stress first some of the variations in the clinical picture of acute rheumatic fever. The classical picture of acute rheumatism is too well known to require repetition but some of its variants may deserve mention. The migratory arthritis may be absent. Von Glahn[36] in a series of 109 cases found 41 "who never had arthritis". There may be only pain and tenderness without swelling. In children the disease tends towards chronicity while in adults the attack is characterized by its explosiveness. According to Swift,[8] "In the adult the arthritis and visceral complications, if they occur, are usually seen within a short period of a few weeks—in children, on the other hand, although the disease is ushered in by an acute onset, the various groups of symptoms may make their appearance months apart." In the latter, nervous symptoms, chiefly the manifestations of chorea, are likely to occur. These may consist simply of nervousness, irritability and clumsiness, or the jerking movements typical of the disease. Frequently observation over a considerable period is necessary in order to establish a diagnosis.

The importance of pulmonary and pleural involvement in rheumatic carditis should be stressed. A left sided fibrinous pleurisy (near the heart) occurs in from 5 to 10 per cent of cases. Pneumonia may mask the picture of rheumatic fever, a condition I described in 1928 under the title of Occult Rheumatism.[51] There has been some discussion as to the occurrence of a specific rheumatic pneumonia. Aschoff bodies have been described[3] in the pulmonary arteries and other characteristic changes in the arterioles of the lung. These pulmonary changes occur more frequently in cases of pancarditis, although they are described as occurring sometimes independent of arthritis or carditis, as in a case reported by myself.[51] It is well to consider this possibility with the occurrence of a "wet pleurisy", for this may be due to rheumatic fever as well as tuberculosis. Paul[52] has recently published a comprehensive review of

the literature on pleural and pulmonary lesions in rheumatic fever.

Subcutaneous nodules occur chiefly in children, rarely in adults. Three types are described: (1) Miliary, in tendons and sheaths; (2) Medium-sized, in broad tendons that pass over joints and at insertions; and (3) Large, over bony surfaces beneath the skin. Nodules usually occur in severe forms of rheumatic infection and have been thought to suggest a poor prognosis; but recently White[10] suggests that they may indicate a favorable reaction. These nodules may be noted late and may not occur on extremities; as in the case of Tredway[23] previously cited, in which they appeared at the end of the twelfth week and were present on the scalp only.

The rash in rheumatic fever (Erythema multiforme) may come in crops with each new involvement of the joints. This occurs at some period in about 15 per cent of the cases; but this sign, as well as the nodule, is less frequently observed in this country than in England. Less frequent skin manifestations are erythema nodosum, urticaria, purpura and petechial hemorrhages. These are the most frequent symptoms of heart invasion —only rarely are pain and dyspnea complained of during the acute stage. Later, if symptoms occur, they are those of congestive failure.

Disturbances of Rhythm. Swift[8] states that 20 to 30 per cent have transient conduction disturbances. Auricular and ventricular premature contractions are frequent. Auricular fibrillation and flutter, also heart block, are serious complications. Mackenzie[40] cites as a rarity a case of auricular fibrillation in a child of five years suffering from rheumatic fever. Associated with these, Neuhof[61] describes "thumpings" occurring with a normal rate, thought by him to be due to "abnormally strong ventricular contractions", and describes also sensations of weight and pressure on the chest not unlike the anginoid pains described by Allbutt. These precordial sensations, except as found in the psychoneurotic type of patient, surely indicate myocarditis or the aortic involvement described by Allbutt.

Pulse. The pulse without heart complications is proportional to the temperature. A high pulse after the disappearance of arthritis is strong evidence of carditis. A slight acceleration of the pulse may precede by several days the physical signs of endocarditis.

Murmurs. Prior to the appearance of a murmur the heart sounds may be muffled due to edema of the valves or may be increased due to ventricular hypertrophy. A systolic murmur without persistent cardiac enlargement and regardless of transmissions is insufficient evidence of organic mitral insufficiency—for even functional murmurs may be heard in the back.

Conclusive signs of stenosis only appear after fibrosis and contraction, which is months after the initial infection. Mitral stenosis, rheumatic in origin, may show only a systolic murmur while the heart is beating slowly. If the rate be increased by exercise or by some drug (amyl nitrite) a diastolic murmur may be heard; likewise a mid-diastolic murmur may be heard only in the recumbent posture. In the absence of a murmur in

diastole, early, mid-, or late, or a definite presystolic murmur, the need of special investigation should always be suggested by a history of chorea or rheumatic fever when there is an unusually sharp first sound, a systolic murmur which begins abruptly, an increased or doubled pulmonary second sound—especially when the second sound at the apex is diminished in intensity—and by the presence of auricular fibrillation or a break in compensation not due to some other cause. Any loud apical systolic murmur in childhood warrants a careful search for signs of mitral stenosis.

Pericarditis. This is not of itself painful; with the onset of temperature and pulse increase one should look for a rub, but because of the evanescent character of pericardial rubs the failure to demonstrate one does not preclude pericarditis.

Cardiac hypertrophy, disproportionate, or not explained by other lesions, suggests adhesive pericarditis. An absence of shifting with postural changes noted in the fluoroscope and electrocardiogram are further evidences of adherent pericardium, but some of the other signs usually associated with adherent pericardium may have a different cause. Systolic retraction at the apex and sternum may be due to right ventricular hypertrophy. Pulsus paradoxicus (waxing and waning with respiration) is present in myocardial insufficiency and in many normals. Diastolic collapse of cervical veins (Friedrich) is not characteristic, since it is seen also in auricular fibrillation. Broadbent's sign may be due to an enlarged heart pulling on its attachments to the diaphragm.

Fever. A temperature of 102° to 104°, if this increase occurs without new joint involvement, suggests visceral involvement. Light fever for weeks or months after the acute symptoms is strong evidence of cardiac involvement, especially when accompanied by leucocytosis.* The lesion may be in the myocardium or mural endocardium.

Sudden pallor, restlessness and nausea, pulse increase with albuminuria and liver enlargement in the course of, or subsequent to, rheumatic fever strongly suggest shock due to splanchnic dilatation.

Prognosis

This depends upon the age at which the initial infection occurs and the frequency of recurrence of rheumatic infection. With a slight lesion, protection throughout life, and luck, the individual may carry a rheumatic valve lesion with very little if any disability and reach the normal life expectancy; but more frequently cardiac sequelae cripple the patient for years before he finally succumbs.** Cohn[53] stated that an average period of fifteen years

*Recent studies indicate that the sedimentation rate may serve as a useful indication of existing cardiac infection.

**In a recent article Morse[64] analyzes 100 consecutive cases of acute rheumatic (?) endocarditis, seen in the first attack and followed over a period of 10½ to 26½ years, and comments on the relatively small number of deaths (36), the small number of cardiac invalids (3), and the large number of complete recoveries (61). Of this group of 61 cases who had completely recovered, Morse found 37 in whom the hearts appeared normal on examination. Even allowing for a certain small factor of diagnostic error, this percentage of apparently normal hearts is so striking as to merit comparable studies by other competent observers.

elapses between the initial attack of acute rheumatic fever and the death of the patient from the resulting heart disease. Christian[54] places a comparable figure at twenty years and White[10] at ten to twenty years. In adult life there is much less likelihood of additional rheumatic valve involvement due to recurrent rheumatic infection, but far greater danger of auricular fibrillation, with the frequently resulting congestive heart failure, and of a *Streptococcus viridans* infection as an added insult to the existing rheumatic endocarditis. Patients with aortic valve lesions or mitral lesions which are predominantly regurgitant are somewhat more prone to viridans infection than are those with mitral stenotic lesions. Most important is the certainty of progression in the mitral stenotic lesions. Allbutt states that pericarditis in an adult always carries with it a poor prognosis.

Complications

Congestive heart failure, auricular fibrillation and subacute bacterial endocarditis (*Streptococcus viridans*) constitute the most important complications. Congestive heart failure occurs in at least two-thirds, fibrillation in one-fifth and viridans infection in 4 per cent of all cases of rheumatic carditis according to figures furnished by White.[10]

Treatment

Salicylates. Regarding the treatment of rheumatic fever Swift[8] advised us to obtain the maximum effect of salicylates to the point of beginning toxicity, rest one day and then give a smaller dose. Crummer[32] felt that cases properly treated show less tendency to pericarditis and "endocardial changes" and tend to earlier stabilization. Leech[55] believed there is a definite advantage in giving daily rations of salicylates to children who represent actual or potential instances of rheumatic heart disease. There is no evidence of any effect of the drug on the slowly progressive development of mitral stenosis.

While Mackenzie[40] taught that there is a specific action of the salicylates on the rheumatic heart, the general opinion appears to be that this drug is less efficient in its action on the heart than on the joint tissues. This difference in response on the part of different tissues has some experimental basis. Hagebush and Kinsella[56] showed that the allergic dermal reactions produced in rabbits in the course of chronic focal streptococcal infection could be entirely prevented by salicylates, while the vascular lesions remained unaltered. Small[57] stated that there is a difference in response to salicylates in the proliferative (heart) and exudative (joint) lesions. Wyckoff[43] showed that salicylates have no effect on the A-V conduction time. It would seem that the prophylactic use of salicylates during any acute respiratory infection might be of value in reducing the number of cases of rheumatic fever and hence of rheumatic carditis. Quite recently it has been shown[58] that by the simultaneous administration of magnesium sulphate or chloride (grams 2 to 4) and salicylates there is a distinct augmentation of the effect of the latter. This process is described as potentiation and is comparable to that observed when magnesium salts are administered with morphine.

Digitalis. Schwartz[59] stated that in

childhood nausea and vomiting occur as a late manifestation of digitalis action, whereas slowing of the sinus rate occurs early but is a transitory phenomenon, never lasting more than four to seven days. If digitalis is pushed further, block occurs. He believed that nausea and vomiting cannot be safely used as criteria of digitalization in rheumatic valvular heart disease with failure. Schwartz also said that digitalis in adequate doses can produce both the transient and permanent forms of auricular fibrillation in children with heart disease. This may be an early manifestation of its toxic effect and may result fatally. He concluded that digitalis is contraindicated in children with rheumatic fever and signs of cardiac insufficiency. Allbutt[38] advised against digitalis in the acute stage.

Levy and Golden[60] suggested roentgen therapy in rheumatic carditis. They believed this modifies the lesions, basing their opinion upon alterations in the form of the electrocardiogram, and felt that in thirty cases of rheumatic heart disease the clinical course was apparently influenced in twenty-one. In their article I find no mention of similar electrocardiographic observations in a control series—as in a series of noncardiac cases—a point of considerable importance since roentgen exposure is known to cause changes in the heart muscle.

Clawson[25] showed that "lesions similar to those found in rheumatic fever can be produced in animals" by the injection of streptococci and that animals so sensitized can be protected from these rheumatoid lesions by intravenous streptococcus vaccination. He concludes that since rheumatic fever patients are hypersensitive to streptococci, intravenous vaccination with streptococci "may be indicated in acute rheumatic fever".

Swift,[16] et al., in a recent article presented a very complete review of vaccination with streptococci in rheumatic fever. They advanced a working hypothesis which assumes hypersensitiveness to streptococci associated with continuous or repeated low-grade focal infection. If at any time an acute infection supervenes—as tonsillitis, or sinusitis—this hypersensitiveness increases. They stated, "These irritants appear to attack those mesenchymal tissues most subject to physiological trauma; hence lesions commonly occur in such constantly moving structures as joints, tendons, heart and blood vessels". They further stated, "In patients with active disease, both febrile and focal reactions following vaccination have many resemblances to true rheumatic relapses and that these can either be prevented or terminated by anti-rheumatic drugs, is highly suggestive"; and that "the sensitization responsible in part for the pathogenesis of rheumatic fever was induced by strains closely related to hemolytic streptococci".

Discussing the advantages of intravenous over subcutaneous vaccination they show that in animals the "injection of streptococcal vaccines into the tissues usually tends to sensitize, while intravenous injections tend to diminish the overactivity of hypersensitive tissues, and therefore the logical method would be intravenous inoculation under proper precautions". In addition the local reactions about the

site of subcutaneous vaccination with streptococci are often so intense that patients are unwilling to have them repeated. Intravenous injections, on the other hand, are free from local reactions, and most patients are willing to continue them for a full course; hence, from both a theoretical and practical point of view, the intravenous route is the one of choice. This form of treatment Swift considered especially applicable to two classes of patients: (1) Those with a continuing low-grade infection; and (2) those temporarily free from symptoms, but in whom relapses may reasonably be expected. They seem to show a distinct result from the intravenous administration of a vaccine made from hemolytic streptococci: "In about four-fifths of the patients increasing tolerance to the vaccine was accompanied by improvement".

Discussing treatment by means of vaccines, anti-sera and soluble products of bacteria, Small[57] stated that there are three main methods of attack upon the tissues in rheumatic fever: (1) Local growth of streptococci, (2) General toxic effect of streptococci, (3) Other bacterial products distributed from a focal source and capable of inducing and maintaining the allergic state. Probably these seldom act singly. Small's working hypothesis assumed that the visceral (vascular and cardiac) lesions on the one hand and the joint lesions on the other are caused by a different mechanism. The former are due to a specific endotoxin, the latter to the establishment of hypersensitiveness to a protein fraction contained in numerous streptococci, an example of the production of a specific allergin of diverse biologic origin. "The problem in therapy of acute rheumatic fever appears to be that of complete neutralization of the toxic factor by a specific antiserum without passively transferring to the patient hypersensitization to the protein antigen common to different streptococci." The focal reaction in joints following the administration of Small's antiserum is a manifestation of this passive transfer of allergy, therefore the protein fraction must be removed. To accomplish this he uses his "soluble antigen".

In the treatment of rheumatic fever and its visceral complications Small[22] reported results in 1928 as follows:

There were prompt beneficial effects in 251 patients with chorea and acute rheumatic fever. In these were acute arthritis, endocarditis, myocarditis, pericarditis, pleuritis, pneumonitis and subacute nodules. In chorea the twitchings subside promptly and usually disappear in one week. This serum should be used as early as possible and is not contra-indicated by carditis. If the patient is sensitive to horse serum Small furnishes a bovine antiserum following the administration of which severe urticaria, febrile reactions and arthralgia are less common. Further, to prevent severe reactions, the serum is given in divided doses to patients acutely ill.

Vaccines proved to produce reactions in deep seated rheumatic infections, so were discontinued in favor of soluble antigen, but this was not used except as a followup treatment after the antiserum, and as a prophylactic it is again given in the spring and fall for several years, giving six to twelve injections with each series. Small

especially emphasizes the importance of avoiding noteworthy reactions.

From the foregoing it will be evident that, although a great deal of work has been done along the line of biological treatment of rheumatic fever in its various manifestations, there is no uniformly accepted biological treatment.

Rest. The chief method of therapeutic attack in rheumatic carditis has been left to mention last. Complete bed rest at the earliest appearance of any manifestation of rheumatic fever and until all evidence of any type of acute rheumatic involvement is past will offer the greatest assurance of prevention of extension of the process to the heart, if this be possible, and if not will furnish the greatest surety of a limitation of that process and a minimum of cardiac damage.

Rheumatic carditis ordinarily dates from childhood rheumatism. Every rheumatic child, if not actually, is potentially a cardiac patient. Even in the absence of demonstrable carditis the child with rheumatic fever or chorea should be treated as a cardiac patient, which means primarily rest over a long period. With such a treatment the physician will cure many early cases of cardiac rheumatism and, if not so fortunate, will at least prevent many of the sequelae which determine whether the child should enjoy comparative health or invalidism.

Prevention of rheumatic carditis. The foregoing paragraph probably embraces all that we know definitely regarding the subject. Rheumatic fever appears to be a communicable disease with about the same tendency to family infection as has tuberculosis. Presumably the prevention of upper respiratory tract infection will in the future materially reduce the incidence of rheumatic fever and rheumatic heart disease.

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Early Manifestations of Rheumatic Infections in Young Children*

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THE early manifestations of rheumatic infections in children are characterized by an insidious onset. Such children are pale, easily fatigued, have poor appetites and are not gaining in weight as they should. Many complain of slight pains in the legs, feet or joints. There is often stiffness of limbs or neck. Digestive disturbances with paroxysmal abdominal pains are common. There is a change in disposition. The children become irritable, nervous, peevish and are easily frightened. Often there is a failure in mental concentration and they begin to drop objects and at times have difficulty in writing. There may be slight muscle twitching. Examination shows an anemic child who is irritable, nervous, excitable, high strung and usually underweight.

The second heart sound is accentuated, with a soft blowing systolic murmur heard over the apex, that may or may not be transmitted. When the murmur is heard in a patient in whom it did not previously exist and is known to remain constant for at least a month, during which time the patient is free of temperature and acute infections, the diagnosis of a rheumatic infection is almost certain. Often no murmur is heard, but the heart action is rapid and the apex impulse exaggerated.

In the registration area[1] the death rate from organic heart disease has been increasing gradually for a long series of years. In 1910 in New York City,[2] the death rate due to heart disease was 175 per 100,000 population. In 1925 the rate was 266 per 100,000 population, showing an increase of 34 per cent. Drolet tells us that heart disease in New York is now responsible for more than one-fifth of the total deaths.

Wyckoff and Lingg[3] analyzed 1000 cases of heart disease and found 25 per cent to be rheumatic, 40 per cent arteriosclerotic, 10 per cent syphilitic and 10 per cent of unknown etiology.

Munly[4] analyzed 1300 cases of heart disease and found that the rheumatic type comprised 35 per cent of the total, arteriosclerotic, 33 per cent; syphilitic, 8.5 per cent; unknown, 20 per cent. Of the unknown group it is believed by most investigators, that they are chiefly of rheumatic origin, the

*Read before the Chattahoochee Valley Medical and Surgical Association, Radium Springs, Ga., July 14, 1931. Received for publication, October 22, 1931.

heart condition being the only manifestation of the rheumatic infection.

In the registration area in the United States in 1928 in children between the ages of 5 and 15 years, rheumatic infections and their complications caused as many deaths as any disease, with the exception of the various types of pneumonia.[5] The American Heart Association stated, "if present conditions continue, one in every five of population living at age 10 will die of heart disease."

Feer[6] stated that 80 or 90 per cent of all cases of rheumatic infection will have a certain degree of heart involvement. Riesman and Small[7] stated that cardiac involvement is part and parcel of the rheumatic process and is no more a complication or sequella than is the involvement of the shoulder joint a day or more after that of the knee. Coombs[8] states, "The heart may be damaged without manifestations of the infection. Every child that has rheumatic polyarthritis, which can be recognized as such, may be assumed to have an affected heart." Still[9] in his excellent book wrote, "There is no more pitiful sight than seeing a child dying from rheumatic carditis. It is hoped that by recognition of these cases in the early stage, that some of the terrible results can be prevented."

It has been found that heart disease reduces the span of life by practically one-half. It is a well known fact that an established heart lesion in the early stages can often become stationary by the cooperation of the patient who receives the proper medical supervision and instruction. Rheumatic infections are thought to be responsible for approximately 40 per cent of the total cardiac deaths, the majority of the patients contracting the heart condition in early childhood.

From the above observations and statistics it seems logical that the way to reduce the mortality from rheumatic heart disease is to prevent its development in every way possible. If every child with early manifestations of rheumatic infection was considered a potential cardiac patient and managed accordingly, and the parents and patient educated to the danger of the condition, the mortality from rheumatic disease would be reduced in both childhood and adult life.

The following is a report of clinical observations in 258 patients, observed in private practice, with early manifestations of rheumatic infections. Of this number 132 were boys and 126 girls. One hundred eighteen of the patients were reported in 1929.[10] The largest number of cases were seen in the late winter and early spring. Fifty-eight per cent of the patients were seen in the months of January, February, March, and April. The largest number of cases were seen in March.

The following are the ages when the children were first seen with manifestations of the infection: 75 between 2 and 5 years; 86 between 5 and 7, and 97 after the age of 7 years.

Every patient had all or some of the following symptoms: They were pale, high strung, nervous, irritable children, easily fatigued, with poor appetites, who were either losing weight or not gaining as they should. Two hundred three, or 80 per cent, gave histories of repeated attacks of tonsillitis. Two hundred two, or 78 per cent, had soft blowing systolic heart murmurs. No child is included in this

series as having a heart murmur, except those patients in whom the murmur was known to exist and remain constant for at least one month, during which time the child was free of temperature and acute infections.

One hundred seventy-five, or 68 per cent, gave histories of pains in the extremities or stiffness of the joints. One hundred fifty-four, or 60 per cent, were 7 per cent or more underweight for height. Seventy-one, or 28 per cent, gave histories of digestive disturbances characterized by paroxysmal abdominal pains. In 70, or 27 per cent, there were signs and symptoms of a mild chorea. Of this number 38 were girls and 32 boys. Many gave histories of night terrors, enuresis and tachycardia.

TABLE 1
The Number of Children and the Percentage Underweight for Age and Height

Percentage Underweight	For Age No. Patients	For Height No. Patients
1- 6	63	60
7-10	36	50
11-14	33	50
15-20	25	39
21-25	7	15
Over 25	4	0
Total	168	214

FOCI OF INFECTION

In young children apparently the foci of infection were largely in the tonsils, nasopharynx and teeth. Foci of infection were thought to be located as follows:

126 cases, tonsils and adenoids;
49 cases, teeth or both teeth and tonsils;
21 cases, chronic nasopharyngitis or paranasal sinusitis;
62 cases, undetermined.

One hundred twenty-six, or 50 per cent, of the total number of children were known to have manifestations of rheumatic infections before the tonsils and adenoids were removed. Of this number 114, or 90 per cent, developed systolic heart murmurs. There were signs and symptoms of a mild chorea in 11 per cent. In 29 cases in which the teeth alone were thought to be the foci of infection, heart murmurs were present in 38 per cent and signs of chorea in 62 per cent. In 20 cases in which both the teeth and tonsils were apparently the foci of infection, heart murmurs were present in 75 per cent, signs of chorea in 55 per cent. Twenty-one cases in which the nasopharynx and paranasal sinuses were thought to be the foci of infection, were either irregular patients or cases having the tonsils and adenoids removed before being seen. In the majority there were histories of repeated attacks of tonsillitis.

Of the 62 cases in which the foci of infection were undetermined, heart murmurs were present in 79 per cent, signs of chorea in 30 per cent. In the majority of these cases the tonsils and adenoids were removed before the patient was seen. In many, before the operation, there was a definite history of rheumatic infections. Approximately 75 per cent gave histories of repeated attacks of tonsillitis. Otitis media was a very common occurrence. Many of the children had signs and symptoms suggestive of a paranasal sinusitis.

Ninety-one patients, 52 boys and 39 girls, developed heart murmurs while under observation. In 54, or 59 per cent, of the cases the murmur was first heard between the ages of 3 and 6 years. A diagnosis of chronically diseased tonsils and adenoids was

TABLE 2
Summary of Clinical Observations in 258 Patients with Early Manifestations of Rheumatic Infections, with Grouping According to the Apparent Foci of Infection

Foci of Infection	No. Patients	Heart Murmurs		Pains in Ext. or Stiffness of Joints		Pains in Abdomen		Sympt. and Signs of Chorea	
		No.	Pts. %	No.	Pts. %	No.	Pts. %	No.	Pts. %
Tons. ad. Nasopharynx	126	114	90	84	67	40	32	14	11
Teeth, tonsils Ad. nasophar.	20	15	75	15	75	4	20	11	55
Teeth	29	11	38	19	66	5	17	18	62
Nasophar. paranas. sinus, etc.	21	13	62	18	86	7	33	8	38
Undetermined	62	49	79	39	63	15	24	19	31
Total	258	202	78	175	68	71	28	70	27

made in 93 per cent of the cases. Eighty-five per cent were seen one or more times with attacks of acute follicular tonsillitis. From 1 to 2 years before the murmur was heard, 39 per cent of the children were 7 per cent or more underweight for height. At the time of murmur the number had increased to 49 per cent. In 69, or 76 per cent, of the children the murmur was heard before the tonsils and adenoids were removed. No murmur was heard in 22, or 24 per cent, of the cases until after the operation. In 6 of these 22 patients, a diagnosis of a rheumatic infection had been made before the removal of the tonsils and adenoids. Eight cases were seen at irregular intervals and it is possible that the children had the heart murmur before the opration. At the time of murmur, 30 patients gave histories of pains in the extremities. Six were treated for pains in legs before murmur was heard. Ten cases, at the time of the murmur with negative histories, developed symptoms later.

Thirty-three, or 36 per cent, of the children had digestive disturbances characterized by paroxysmal abdominal pains, the majority were of such severity that the patients were brought to the office for treatment.

CHOREA

At the time murmur was heard, 3 of the children had signs and symptoms of a mild chorea. From 1 to 4 years after the diagnosis of a rheumatic infection, 6 patients developed symptoms of a mild chorea. In 4 of the 6 cases the teeth were apparently the new foci of infection.

Twenty-four children developed signs and symptoms of a more or less chronic paranasal sinusitis after the removal of the tonsils and adenoids. In these cases there was little improvement in either their physical condition or the rheumatic infection.

LABORATORY FINDINGS

At the time the children were first seen with manifestations of rheumatic infections, white blood counts were made in 167 patients. The lowest count was 4,000; highest, 31,000; average, 11,101. Fifty-eight per cent of the counts were between 9,000 and 12,000. Differential blood counts made in 175 patients showed the

neutrophile percentage above average for the age in 61 per cent of the cases. In 33, or 30 per cent, the neutrophiles were from 15 to 35 per cent above the normal average for patients of the same age.[11]

Hemoglobin estimations were made in 177 patients (Dare and Talquist). The lowest reading was 40 per cent; the highest, 90 per cent; average, 66.7 per cent. One hundred fifteen, or 65 per cent, of the readings were between 40 and 70 per cent. One hundred sixty-seven, or 94 per cent, were between 50 and 80 per cent.

TABLE 3

Hemoglobin Percent	No. Cases
40-50	5
50-60	31
60-70	57
70-80	53
80-90	31
Total	177

Red blood counts were made in 42 patients. There were 18, or 43 per cent, of the blood counts between 3 and 4 million, 52 per cent between 4 and 5 million, and 5 per cent over 5 million.

Our records show urinalysis in 222 of the patients. In 23 cases albumin was present, casts were found in 4, only 3 of the children proved to have a nephritis. One child was found to have a pyelitis.

Wassermann tests made in 139 children were negative.

Tuberculin tests, intracutaneous and Craig's modification of the Von Pirquet tuberculin test, were done in 198 of the patients. Fifteen, or 7 per cent, gave a positive reaction.

COMMENT

The medical profession considers tuberculosis as either active or inactive and the patient is treated accordingly. The same should be true of rheumatic infections.

Rheumatic fever and other manifestations of the infections are characterized by repeated recurrent attacks. We have often seen cases free of symptoms for months; but when the resistance of the child was lowered from any of the following causes, (1) overwork, (2) fatigue, (3) too much excitement, (4) acute infections, (5) development of new foci of infection, or (6) re-infection of old foci, new manifestations of the rheumatic infection developed.

Many of the patients seen with rheumatic carditis in both young and late adult life, had evidently contracted the disease in early childhood before their tonsils and adenoids were removed. In cases seen with manifestations of rheumatic infection before the tonsils and adenoids were removed, a large percentage developed systolic heart murmurs and a small percentage had signs and symptoms of chorea. In the cases in which the teeth were apparently the foci of infection, the nervous symptoms were more pronounced, usually the heart action was rapid and the apex impulse exaggerated. There were fewer systolic heart murmurs and a decided increase in the number of children with signs and symptoms of mild chorea.

In 9 children heart murmurs were apparently the only manifestations of the rheumatic infection. Six cases between the ages of 2 and 4 years had been seen repeatedly with attacks of acute follicular tonsillitis. Loud, blow-

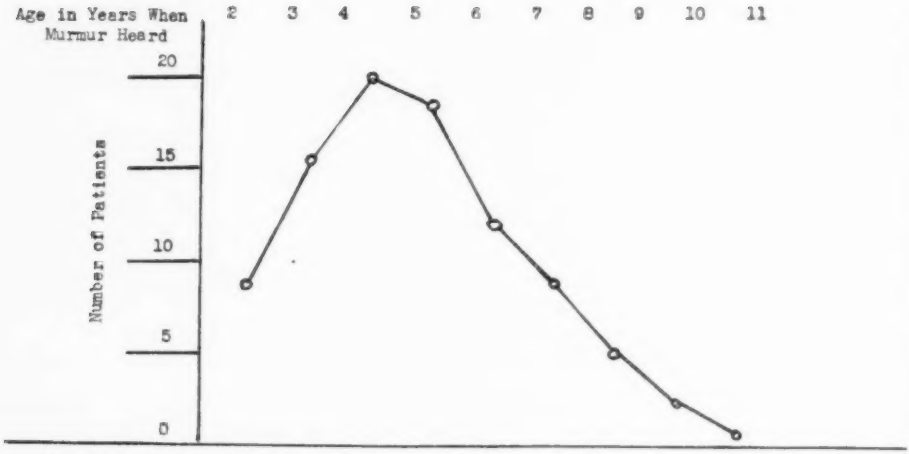

FIG. 1. The age curve of 91 patients with heart murmurs who developed the condition while under observation.

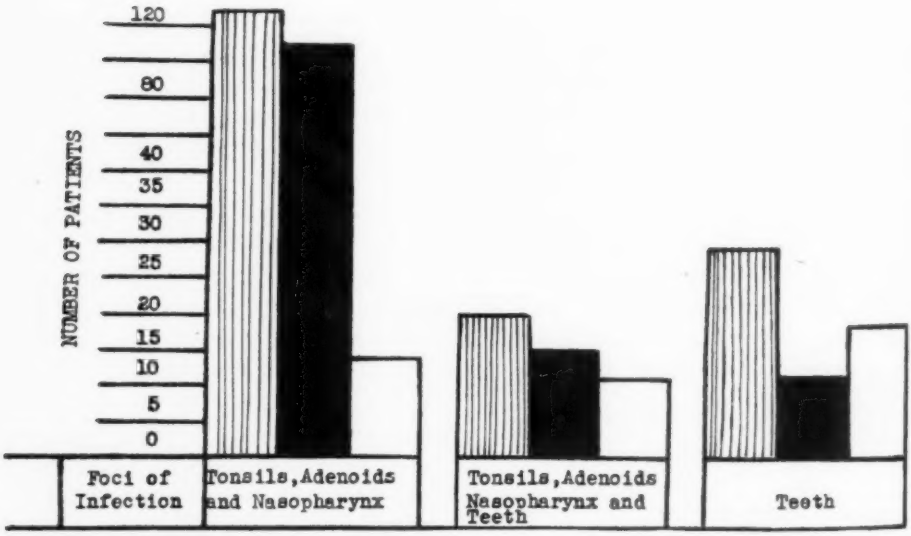

FIG. 2. The incidence of heart murmurs and signs and symptoms of chorea in patients in whom the tonsils, adenoids, nasopharynx and teeth were apparently the foci of infection.
Shaded column—number of patients.
Black column—number of patients with heart murmurs.
White column—number of patients with signs and symptoms of chorea.

ing systolic heart murmurs were discovered in each case between attacks of tonsillitis. The tonsils and adenoids were removed and the murmurs have remained constant for a period of from 2 to 5 years.

Three children who did not look acutely ill or toxic, ran high and widely fluctuating temperatures for several weeks, with negative physical and laboratory findings. Later, in each case, loud blowing systolic heart murmurs developed.

In the cases reported, apparently there was little or no hypertrophy of the heart. In x-ray study, the teleoroentgenogram measurements in the majority of cases taken were within the normal limits. In fluoroscopic examinations, in a few cases there was a definite prominence in the region of left auricle making the left border of the heart almost a straight line.

During the period of observation, in the majority of the instances in which the cooperation of the parents and children was obtained, the heart murmurs have remained constant, with little or no change. In a certain number of cases the heart condition has progressively grown worse. In a small percentage of cases the murmurs have apparently disappeared.

Many children made little or no improvement after the tonsils and adenoids were removed. This was especially true in cases known to have had chronically diseased tonsils and adenoids. The children who did not respond to the operation, almost invariably developed signs and symptoms suggestive of a paranasal sinusitis. The most characteristic symptoms in the order named, follow: (1) The tongue is coated and breath often bad; (2) the uvula is enlarged, swollen and edematous, stretching into a narrow thread like projection clinging to the back of the throat; (3) when the patient is made to gag and contract the muscles of the nasopharynx, a muco-purulent discharge is seen; (4) intermittent cough, paroxysmal in type of several weeks or months duration, the cough being worse at night; (5) the retropharyngeal glands, especially behind the posterior tonsillar pillar are usually enlarged.

Due to the severity of paroxysmal abdominal pains caused by a demonstrable spasmodic contraction of the intestines in 24 children between the ages of 3 and 7 years, a diagnosis of enterospasm was made. The patients were given atropine. Sixteen of the cases at the time of diagnosis had symptoms or signs of a rheumatic infection. Three of the patients later developed manifestations of the infection. The records show a diagnosis of chronically diseased tonsils and adenoids in 16 of the 24 cases.

So many of the patients were seen with otitis media and asthmatic bronchitis that the records were investigated to see if children with manifestations of rheumatic infections had been more susceptible to respiratory infections than children with no manifestations. The number of respiratory infections seen in 84 patients over an exact period of 5 years from the date of birth, is tabulated in Table 4. The infections are listed as mild and severe. The mild infections include ambulatory cases with little or no temperature, comprised principally of mild upper respiratory types of infections. The severe infections include bed cases, acutely ill with high tempera-

ture, comprised principally of so-called influenza with its various complications, acute bronchitis, acute follicular tonsillitis, etc.

TABLE 4
The Number of Respiratory Infections Seen in 84 Patients for an Exact Period of Five Years from the Date of Birth

	No. of Pts.	No. of Resp. Inf.			Aver. No. Resp. Inf. per Pt.		
		Mild	Severe	Total	Mild	Severe	Total
Pts. with mans. of Rheumatic inf.	23	81	139	220	3.52	6.04	9.56
Pts. without mans. of rheumatic inf.	61	232	376	608	3.8	6.16	9.96

Twenty-three of the 84 patients had manifestations of a rheumatic infection; 61 patients had no manifestations of a rheumatic infection. The average number of respiratory infections per patient for an exact period of 5 years from the date of birth in the rheumatic cases, was 9.56; non-rheumatic cases, 9.96. The rheumatic cases had 3.52 mild and 6.03 severe infections. The non-rheumatic cases had 3.8 mild and 6.16 severe infections.

MANAGEMENT

Every effort is made to keep the child's attention from the heart. The patients are never told they have a cardiac condition. In the management of children it is essential to obtain the confidence and cooperation of the parents by educating them to the danger of the condition.

Every child with manifestations of an early rheumatic infection is given the benefit of the doubt and treated accordingly. What is thought to be the focus of infection is found and removed when practical. Satisfactory results are often obtained by local treatment of the focus. Rest in bed and forced feeding are very important. The children should have from 11 to 12 hours sleep. They are dressed warmly and not allowed out of the house on cold, damp days. They do much better in warm, dry climates than in cold, wet ones. The danger of acute infections should be explained to the parents and the children protected in every way possible.

Our routine when the patient is first seen with early manifestations of rheumatic infections, is to keep the case in bed with the exception of four hours each day, for a period of two to six weeks. During the four hours a day out of bed, the child is usually allowed to do as he pleases, no restrictions being made if possible. They are given a well balanced, six meal diet, with especial emphasis on liver, spinach, prunes, whole wheat breads, and cereals. They are also given malt, iron, and cod liver oil.

One hundred forty-four patients given rest treatment and forced feeding for 518 weeks gained 486 pounds. The average number of weeks of forced feeding and rest treatment per patient was 3.5 weeks. The average number of pounds gained per patient was 3.4 pounds. There was an average gain per patient of 15 ounces per week.

The strain of the long hours of school routine is too great for the average child with a well developed

TABLE 5
One Hundred Forty-Four Patients Given Rest Treatment and Forced Feeding for 518 Weeks, Gained 486 Pounds

	No. of Weeks									Aver. No. of Wks. per Pt.	Aver. No. lbs gained per Pt.	Aver. gain in Oz. per Wk. per Pt.
Rest treatment and forced feeding	1	2	3	4	5	6	7	8	9	3.5	3.4	15
Number of pts.	9	42	29	28	12	13	1	9	1			

rheumatic infection. It was found necessary to remove many children from school two or three times each year and give rest treatment and forced feeding. The physical condition of certain children was such that they could attend school but half a day.

SUMMARY

1. Organic heart disease causes more deaths in the United States than any other condition. Of the total cardiac deaths, approximately 40 per cent are thought to be of rheumatic origin. In a majority of cases the disease is contracted early in childhood.

2. Of 258 patients with early manifestations of rheumatic infections, 126 were girls and 132 boys. One-third of the total number of cases were first seen with manifestations of the infection between the ages of 5 and 7 years.

3. Of the children, 203, or 80 per cent, gave histories of repeated attacks of tonsillitis.

4. Two hundred two, or 78 per cent, had soft blowing systolic heart murmurs.

5. One hundred seventy-five, or 68 per cent, had pains in the legs, joints, or stiffness of the limbs.

6. Seventy-one, or 28 per cent, gave histories of digestive disturbances, characterized by paroxysmal abdominal pains.

7. In 70, or 27 per cent, there were signs and symptoms of a mild chorea. Of this number 38 were girls and 32 boys.

8. Two hundred forty, or 82 per cent, were underweight for their height. For the age, 168, or 63 per cent, were underweight.

9. Ninety-one patients, 52 boys and 39 girls, developed heart murmurs while under observation. In 58 per cent of the children the murmurs were first heard between the ages of 3 and 6 years.

10. In 126 patients, 50 per cent of the total number, the tonsils and adenoids were thought to be the foci of infection; 114, or 90 per cent, developed heart murmurs; 14, or 11 per cent, had signs of chorea.

11. Of 49 cases in which the teeth were apparently the only foci, or one of the foci of infection, 26, or 53 per cent, had heart murmurs; 29, or 59 per cent, had signs of chorea.

12. In 177 patients the average hemoglobin reading was 67 per cent.

13. The incidence and severity of respiratory infections, during the first five years of life, were apparently no

greater in the rheumatic than in the non-rheumatic children.

14. The patients in whom the results from tonsillectomy and adenoidectomy were disappointing, almost invariably developed signs and symptoms suggestive of a paranasal sinusitis. This was especially true in the cases known to have had chronically diseased tonsils and adenoids.

15. During the period of observation in the majority of instances in which the cooperation of the parents and children were obtained, the heart murmurs have remained constant with little or no change. In a certain number of cases the heart condition has progressively grown worse. In a small per cent of cases the murmur has apparently disappeared.

16. One hundred forty-four patients given rest treatment and forced feeding for a period of 518 weeks, gained 486 pounds, an average gain per patient of 15 ounces a week.

Conclusions

Every child with early manifestations of rheumatic infections is a potential cardiac patient and should be managed accordingly.

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Causes, Classification and Differential Diagnosis of Anemias*†

Based on the Detailed Examination of Over Two Hundred Patients and a Study of the Literature

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THIS is a presentation of the views formulated during a seven years' study of the clinical and laboratory phases of anemias and the literature pertaining thereto. Details of the subjects chosen, technic used, and results of the color, volume and saturation index studies are given elsewhere.[1]

It has long been customary to divide anemias into two groups. Under the term primary anemia were included cases of pernicious anemia and, sometimes, chlorosis; and under the name secondary anemia, all others. These names were given as the cause was supposed to be unknown in primary anemias and known in secondary anemias. Since this classification is illogical in that it groups unrelated conditions together and tends to discourage thinking, it should be discarded.

Fundamental Causes of Anemia

Obviously there are only three fundamental causes of anemia:

1. Deficient production of red cells, or of hemoglobin, or of both, either due to lack of materials (chlorotic type) or to lack of active blood-forming tissue (aplastic or myelophthisic type).

2. Abnormally rapid destruction of red cells or hemoglobin, or both, in the body (the hemolytic type, internal hemorrhage, etc., are included in this group).

3. Hemorrhage or loss of red cells and hemoglobin from the body (anemia of blood loss).

As all clinical anemias result from various combinations of these factors, they deserve special study.

1. *Deficient production of red cells.* This is the group about which we know least.

(a) Deficient supply of erythrocyte-building material. Iron, certain other metals, and probably other, as yet unidentified, substances are necessary for the formation of hemoglobin.[2] Hence, it is probable that deficiency in these substances leads to a low color index and more severe deficiency leads to a low saturation index. Deficiency

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†Received for publication, July 30, 1931.

Acknowledgment is due to P. Blakiston's Son & Co., Inc., 1012 Walnut St., Philadelphia, for permission to include in this article excerpts from the Textbook of Laboratory Diagnosis by Edwin E. Osgood and Howard D. Haskins.

in stroma-building materials, the nature and occurrence of which is not known, might lead to a low volume index, or the low volume index might be secondary to a decreased supply of hemoglobin; but this is as yet pure hypothesis. The most effective therapy would be to supply the deficient substances. Chlorosis is the type anemia of this group.

(b) Aplasia of erythropoietic tissue. Here we expect absence of evidences of red cell regeneration. Therefore, reticulocytes, polychromatophilic cells, and nucleated red cells should be absent from the blood stream, and, as the other myelogenous elements are seldom[3] spared*, one would expect, also, leucopenia, affecting chiefly the myeloid cells (granulocytes), and thrombopenia with the associated prolonged bleeding time, delayed clot retraction and hemorrhagic tendency. Certain poisons, especially benzol,[4] are known to produce this syndrome, and it is probable that also some bacterial toxins can produce it. It may be produced by excessive exposure of blood forming tissue to roentgen rays or radioactive substances[5] and in some cases is due to almost complete destruction of marrow by invasion of other tissue (osteosclerotic anemia and rare instances of malignancy). A few cases occur for which the cause has not been determined and they are grouped under the term idiopathic aplastic anemia. The only therapy that can be expected to be effective in the aplastic cases is removal of the cause and restoration of bone marrow function, although blood transfusion may be of temporary benefit. It is theoretically possible that this deficient function might be due to absence of a normal stimulus.

The only compensatory mechanism available to the body to combat decreased formation of red cells and hemoglobin is to prolong the life of those formed (decreased rate of destruction). The evidences of this are decrease in the icterus index below 2.5, decrease in urobilinogen in the stools, and a greater tendency for it to be absent from the urine. It is possible, but by no means certain, that poikilocytosis and microcytosis are evidences of abnormal length of life in erythrocytes. As the same changes in the aplastic type affect the granulocytes, it is to be expected that they also will show evidence of decreased rate of destruction (increased proportion of segmented forms with five or more nuclear subdivisions).

(c) Destruction of bone marrow (myelophthisic anemia). This is usually due to invasion by other tissue (leukemias, myeloma, malignancies involving the marrow, osteosclerosis, etc.) but may be due to extensive

*The extremely rare condition of progressive postinfectious erythrophthisis in which only erythropoiesis is disturbed is the third member of the group of specific bone marrow dysfunctions; agranulocytosis and thrombopenic purpura (some types) are the other two. In aplastic anemia, all three functions are impaired.

It seems probable that these four conditions may be merely different responses of different individuals to different quantities of the same toxins. For example, it is possible experimentally to produce pictures closely simulating any one of these syndromes by varying the doses and the duration of exposure to benzol. A further point suggesting that this is true, is that cases occur showing clinical features intermediate between any two of these conditions.

osteomyelitis. Although there is often an absolute deficiency in marrow, there is a tendency for that near the lesion to be irritated to abnormal activity (evidenced by unusually immature red and white cells in the blood stream) and for uninvolved marrow to be capable of compensatory hyperactivity. Attempts at compensation by decreased blood destruction may also occur. Hence, the characteristic findings are those of the causative disease (leukemia, etc.) plus the presence of immature erythrocytes (reticulocytes, polychromatophilia, nucleated red cells including megaloblasts) and old red cells (poikilocytes, great anisocytosis), immature granulocytes (even back to the myeloblast with a tendency for eosinophils and basophils to increase as well as neutrophils), and old leucocytes (cells with five or more segments), thus giving rise to a very bizarre blood picture. The color, volume, and saturation indices are variable but most often within normal limits. A low icterus index and decreased urobilinogen excretion is present when decreased red cell destruction occurs. Removal of the cause is the only therapy likely to be of benefit.

2. *Increased Rate of Red Cell Destruction within the Body.* This may be due to extravasation of blood (hemorrhage into body cavities or tissues, hemorrhagic infarcts, etc.), to hemolysis (hemolytic poisons, some bacterial toxins, or hypotonicity of the medium, as after distilled water injections, etc.), to destruction of red cells in the blood stream (malaria), to hyperactivity of the normal blood cell destroying mechanisms, to the production by the bone marrow of red cells with decreased resistance to the factors normally tending to destroy them, or to some abnormality in another organ (spleen?) affecting the red cells in such a way as to decrease their resistance.

The evidences of increased rate of red cells destruction will be common to all. These are: an increase in the blood bilirubin (increased icterus index with negative direct van den Bergh reaction and no tendency to bilirubinuria), increase in urobilinogen in the stools and a tendency for it to appear in the urine in abnormal amounts.

If no other factor than increased blood destruction plays a part, there will be evidence of rapid regeneration of cells, because the remnants of the destroyed corpuscles and hemoglobin within the body insure the continuous presence of an excess of erythrocyte and hemoglobin-forming materials*. Hence, one would expect to find in a purely internal blood destruction anemia, an increase in young erythrocytes, other evidences of increased bone marrow activity (neutrophilia with increased proportion of immature forms, and thrombocytosis), and red cells of normal size and hemoglobin content (normal color, volume and saturation indices).

Rapid regeneration of cells by the bone marrow is the compensatory mechanism in this group, and in uncomplicated cases, removal of the cause is the only therapeutic measure indicated, for the body already contains an excess supply of erythrocyte-forming materials, from the destroyed cells.

*It is theoretically possible that interference with the transport mechanism would prevent these from being available at the point where they are needed.

It is further obvious that if regeneration keeps pace with cell destruction, a cause for anemia of this type can exist without the production of an actual anemia, but the evidences of rapid erythrocyte destruction and of rapid erythrocyte regeneration will, nevertheless, be present.

3. *Blood Loss from the Body.* This includes all types of external hemorrhage, as well as hemorrhages from the air passages and gastrointestinal tract, in which blood leaves the body before destruction and reabsorption. Here, evidences of blood destruction will be lacking, but as long as adequate supplies of blood-forming materials are available, evidences of rapid red cell regeneration will be present. Therefore, the pictures for acute blood loss and chronic blood loss will be different.

(a) Acute blood loss. The deficiency in red cells and hemoglobin will not be apparent until increased plasma volume occurs. Compensation is by rapid regeneration from existing stores, so the evidences of increased bone marrow activity (reticulocytosis, polychromatophilia, nucleated red cells, neutrophilic leucocytosis, thrombocytosis) dominate the picture, and cells of normal size and hemoglobin content (normal color, volume and saturation indices) are formed as long as the supplies of stroma- and hemoglobin-building materials are not exhausted. Later, decreased color, volume and saturation indices may occur if the loss of blood was extreme, and decreased blood destruction (low icterus index, poikilocytosis) may occur as a compensatory factor; but these changes are never present in the first few days.

(b) Chronic blood loss. Here the exhaustion of the hemoglobin-building (and probably also of stroma-building) material becomes the dominant factor, and this relative insufficiency gives rise to a picture almost identical with the absolute insufficiency (see 1 (a) above). Thus, evidences of compensatory decreased blood destruction and, to a less extent, of compensatory increased blood formation are both present, but the most characteristic change is a decrease in the color, volume and saturation indices, particularly the latter. Removal of the cause and administration of erythrocyte-forming substances are obviously both indicated. Here, too, it is possible for regeneration to keep pace with loss and, when the total blood volume and the normal rate of regeneration are considered, it is evident that the total quantity of blood lost per day must be very considerable (actual amount undetermined) to produce anemia, if no additional factors are present.

Differential Diagnosis of Anemias

Unfortunately, clinical anemias are usually due to a combination of the above mentioned fundamental causes, and are in many instances too inadequately studied for one to be certain which of these factors plays the major rôle.

In this study much material was accumulated to aid not only in the differential diagnosis of anemias but likewise in the determination of the fundamental factors responsible. It has seemed best to summarize these in tabular form since detailed presentation would exceed the space limits of

	Relative Frequency	Color Index A	Volume Index B	Saturation Index B	Red Blood Cells A Million per cmm.	Hemoglobin A Grams per 100 c.c.	Cell Volume B C.c. per 100 c.c.	Anisocytosis A	Poikilocytosis A	Polychromatophilia A	Reticulocytes 14 B Per cent	Normoblasts A	Megaloblasts A	Fragility of C Red Blood Cells: Begin %NaCl	Fragility of C Red Blood Cells: Complete %NaCl	Icterus Index A	Urobilinogen in Urine B (Dilution in which +)	Urobilinogen in Stool D	White Blood Cells B Thousand per cmm.	Polymorphonuclears % B	Small Lymphocytes % B	Eosinophiles % B	Increase in Immature C Neutrophiles
Normal Men	1	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	4.4 to 6.4	13.5 to 19.0	38 to 50	0	0	0	0 to 1	0	0	0.46 to 0.42	0.36 to 0.30	4.0 to 6.0	0 to + in 1/10	2+	5 to 10	55 to 75	20 to 35	1 to 4	0
Normal Women	2	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	4.0 to 5.6	11.0 to 16.0	35 to 46	0	0	0	0 to 1	0	0	0.46 to 0.42	0.36 to 0.30	4.0 to 6.0	0 to + in 1/10	2+	5 to 10	55 to 75	20 to 35	1 to 4	0
1 Acute Hemorrhage, internal	6	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	2.5 to 6.0	7.0 to 18.0	20 to 50	0 to +	0 to +	+ to 3+	1 to 15	0 to 2+	0 to +	0.46 to 0.38	0.36 to 0.28	6.0 to 30.	0 to + in 1/100	2+ to 3+	10 to 35	65 to 90	5 to 30	0 to 2	+ to 3+
2 Acute Hemorrhage, external	7	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	2.5 to 6.0	7.0 to 18.0	20 to 50	0 to +	0 to +	+ to 3+	1 to 15	0 to 2+	0 to +	0.46 to 0.38	0.36 to 0.28	1.0 to 6.0	0 to + in 1/10	+ to 2+	10 to 30	65 to 90	5 to 30	0 to 2	+ to 3+
3 Malaria	9†	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	1.5 to 4.0	4.0 to 12.0	10 to 35	+ to 3+	+ to 2+	+ to 3+	.1 to 15	0 to 3+	0 to +	0.44 to 0.36	0.34 to 0.26	6.0 to 30.	+in 1/10 to 1/100	2+ to 4+	2 to 10	30 to 70	25 to 65	2 to 12	0 to 2+
4 Apparent Anemia	10	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*	*	*	*	*	*	*	*
5 Intestinal Parasites	11†	0.70 to 1.20	0.70 to 1.20	0.70 to 1.20	1.5 to 6.0	4.0 to 18.0	10 to 50	0 to 3+	0 to 4+	0 to 3+	0 to 5	0 to 2+	0 to 2+	0.46 to 0.36	0.36 to 0.26	1.0 to 6.0	0 to + in 1/10	+ to 2+	5 to 20	20 to 70	20 to 65	2 to 60	0 to 2+
6 Sickle-Cell Anemia	12	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	1.5 to 6.0	5.0 to 18.0	10 to 50	+ to 4+	+ to 4+	+ to 4+	.5 to 5.	0 to 3+	0 to 3+	0.46 to 0.36	0.36 to 0.26	6.0 to 30.	+in 1/10 to 1/100	2+ to 4+	5 to 25	50 to 85	10 to 35	0 to 10	0 to 3+
7 Myelogenous Leukemias	13	0.80 to 1.40	0.80 to 1.40	0.80 to 1.20	1.0 to 8.0	2.5 to 20.0	8 to 55	+ to 4+	+ to 4+	0 to 4+	.1 to 15	0 to 4+	0 to 4+	0.46 to 0.36	0.36 to 0.26	1.0 to 10.	0 to + in 1/30	+ to 2+	2 to 1000	10 to 90	0 to 30	0 to 80	3+ to 4+
8 Lymphatic Leukemias	14	0.80 to 1.40	0.80 to 1.40	0.80 to 1.20	1.0 to 6.0	2.5 to 18.0	8 to 50	+ to 4+	+ to 4+	0 to 4+	.1 to 15	0 to 3+	0 to 2+	0.46 to 0.36	0.36 to 0.26	1.0 to 10.	0 to + in 1/30	+ to 2+	2 to 1000	0 to 60	30 to 99	0 to 1	0 to +
9 Hodgkin's Disease	15	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	1.5 to 5.0	4.0 to 16.0	10 to 45	0 to 3+	0 to 3+	0 to 3+	.1 to 4.	0 to 2+	0 to +	0.46 to 0.36	0.36 to 0.26	1.0 to 20.	0 to + in 1/50	+ to 2+	5 to 25	40 to 90	10 to 55	0 to 30	0 to 2+
10 Lymphosarcoma	16	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	1.5 to 5.0	4.0 to 16.0	10 to 45	0 to 3+	0 to 3+	0 to 3+	.1 to 4.	0 to 2+	0 to +	0.46 to 0.36	0.36 to 0.26	1.0 to 20.	0 to + in 1/30	+ to 2+	5 to 25	40 to 90	10 to 55	0 to 30	0 to 2+
11 Poisoning with Heavy Metals	17	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	2.0 to 6.0	6.0 to 18.0	15 to 50	0 to 2+	0 to 2+	0 to 4+	.5 to 15	0 to 4+	0 to 4+	0.42 to 0.34	0.32 to 0.24	4.0 to 20.	0 to + in 1/50	2+ to 4+	2 to 15	30 to 90	10 to 60	0 to 2	0 to 2+
12 Poisoning with Other Blood Destroying Toxins	18	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	2.0 to 6.0	6.0 to 18.0	15 to 50	0 to 2+	0 to 2+	0 to 4+	.5 to 15	0 to 4+	0 to 4+	0.42 to 0.34	0.32 to 0.24	6.0 to 50.	+in 1/20 to 1/100	3+ to 4+	5 to 25	50 to 90	10 to 40	0 to 4	0 to 3+
13 Myxedema	21	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	2.0 to 6.0	6.0 to 18.0	15 to 50	0 to 3+	0 to 3+	+ to 3+	.1 to 4.	0 to 2+	0 to 2+	0.42 to 0.34	0.32 to 0.24	4.0 to 14.	0 to + in 1/50	2+ to 3+	4 to 10	40 to 70	20 to 50	0 to 4	0
14 Addison's Disease	22	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	3.0 to 6.0	9.0 to 18.0	20 to 50	0 to 2+	0 to 2+	0 to 2+	0 to 3.	0 to 2+	0 to +	0.46 to 0.38	0.36 to 0.28	4.0 to 10.	0 to + in 1/30	2+ to 3+	4 to 10	40 to 70	20 to 50	0 to 8	0 to 2+
15 Aplastic Anemia	26	0.70 to 1.20	0.70 to 1.20	0.80 to 1.20	0.8 to 4.0	2.0 to 12.0	6 to 35	0 to +	0 to +	0	0	0	0	0.46 to 0.42	0.36 to 0.30	0.5 to 15.	0 to + in 1/20	+	0.1 to 3.0	0 to 20	80 to 100	0 to 1	0
16 Hemolytic Icterus	29	0.80 to 1.20	0.80 to 1.20	0.80 to 1.20	2.5 to 5.0	6.0 to 16.0	15 to 45	2+ to 4+	0 to 3+	2+ to 4+	5 to 60	+ to 4+	0 to 4+	0.72 to 0.50	0.60 to 0.40	6.0 to 80.	+in 1/20 to 1/500	3+ to 4+	7 to 20	60 to 85	10 to 30	0 to 6	0 to 2+
17 Pernicious Anemia	5	1.15 to 2.00	1.15 to 2.00	0.80 to 1.20	0.4 to 4.0	1.5 to 18.0	5 to 45	+ to 4+	0 to 4+	0 to 4+	.2 to 60	0 to 4+	0 to 4+	0.44 to 0.38	0.34 to 0.26	6.0 to 20.	+in 1/20 to 1/100	3+ to 4+	1.5 to 14.	30 to 80	15 to 65	1 to 8	+ to 3+
18 Pernicious Anemia of Sprue	19†	1.15 to 2.00	1.15 to 2.00	0.80 to 1.20	0.8 to 4.0	2.0 to 18.0	8 to 50	0 to 4+	0 to 4+	0 to 4+	.2 to 20	0 to 4+	0 to 4+	0.46 to 0.38	0.36 to 0.26	4.0 to 20.	+in 1/10 to 1/50	2+ to 4+	3 to 15	30 to 80	15 to 65	1 to 25	0 to +
19 Pernicious Anemia of *Dibothriocephalus latus*	24†	1.15 to 2.00	1.15 to 2.00	0.80 to 1.20	0.8 to 4.0	2.0 to 18.0	8 to 50	0 to 4+	0 to 4+	0 to 4+	.2 to 20	0 to 4+	0 to 4+	0.46 to 0.38	0.36 to 0.26	4.0 to 20.	+in 1/10 to 1/50	2+ to 4+	5 to 12	50 to 70	20 to 40	0 to 12	0 to +
20 Pernicious Anemia of Pregnancy	27	1.15 to 2.00	1.15 to 2.00	0.80 to 1.20	0.8 to 4.0	2.0 to 18.0	8 to 50	0 to 4+	0 to 4+	0 to 4+	.2 to 20	0 to 4+	0 to 4+	0.46 to 0.38	0.36 to 0.26	4.0 to 20.	+in 1/10 to 1/30	2+ to 4+	5 to 15	40 to 80	20 to 40	0 to 8	0 to 2+
21 Chronic Hemorrhage	4	0.40 to 1.00	0.40 to 1.00	0.60 to 1.10	1.5 to 5.0	2.0 to 12.0	12 to 38	+ to 4+	+ to 4+	0 to 3+	0 to 2.	0 to 2+	0 to +	0.46 to 0.40	0.36 to 0.28	0.5 to 4.0	0 to + in 1/10	+ to 2+	2 to 8	30 to 70	25 to 65	0 to 2	0 to +
22 Dietary Deficiency Anemia	23	0.40 to 1.00	0.40 to 1.00	0.60 to 1.10	1.5 to 5.0	2.0 to 12.0	10 to 38	+ to 4+	+ to 4+	0 to 2+	0 to 1.	0 to +	0	0.46 to 0.40	0.36 to 0.28	0.5 to 6.0	0 to + in 1/10	+ to 2+	2 to 12	30 to 70	25 to 65	0 to 2	0 to +
23 Chlorosis	28	0.40 to 0.85	0.40 to 1.00	0.60 to 1.00	2.0 to 5.0	2.0 to 12.0	10 to 35	+ to 4+	0 to 2+	0 to +	0 to 1.	0 to +	0	0.46 to 0.40	0.36 to 0.30	0.5 to 4.0	0	+ to 2+	2 to 20	40 to 70	25 to 55	0 to 6	0
24 Infections (including Nephritis)	3	0.60 to 1.20	0.60 to 1.20	0.80 to 1.20	2.0 to 6.0	5.0 to 18.0	15 to 50	0 to 4+	0 to 4+	0 to 4+	0 to 2.	0 to 2+	0 to +	0.46 to 0.38	0.36 to 0.28	*	*	*	*	*	*	*	*
25 Malignant tumors (Uncomplicated by Hemorrhage, Secondary Infection, or Bone Marrow Involvement)	8	0.70 to 1.20	0.70 to 1.20	0 80 to 1.20	3.0 to 6.0	6.0 to 18.0	18 to 50	0 to 3+	0 to 3+	0 to 3+	0 to 2.	0 to +	0	0.46 to 0.38	0.36 to 0.28	*	*	*	*	*	*	*	*
26 Cirrhosis of the Liver	20	0.70 to 1.20	0.70 to 1.20	0.80 to 1.20	2.5 to 5.0	5.0 to 18.0	12 to 45	0 to 3+	0 to 3+	0 to 3+	0 to 4.	0 to 2+	0 to +	0.46 to 0.36	0.36 to 0.26	6.0 to 50.	+in 1/10 to 1/500	+ to 3+	2 to 7	30 to 70	25 to 65	0 to 6	0
27 Banti's Disease	25	0.70 to 1.20	0.70 to 1.20	0.80 to 1.20	2.0 to 4.0	4.0 to 12.0	12 to 45	0 to 3+	0 to 3+	0 to 3+	0 to 4.	0 to 2+	0 to +	0.46 to 0.36	0.36 to 0.26	6.0 to 30.	+in 1/10 to 1/500	+ to 3+	1 to 6	20 to 60	35 to 75	0 to 6	0
28 Gaucher's Disease	30	0.70 to 1.20	0.70 to 1.20	0.80 to 1.20	3.0 to 6.0	6.0 to 18.0	18 to 50	0 to 2+	0 to 2+	0 to 2+	0 to 2.	0 to 2+	0	0.46 to 0.36	0.36 to 0.26	4.0 to 20.	+in 1/10 to 1/200	2+ to 3+	2 to 8	30 to 70	25 to 65	0 to 6	0 to 2+

*The results are so variable within the group that they have individual rather than group diagnostic value.
†Incidence very variable in different localities. >=greater than. <=less than. 0=not present.
+=minimal. 4+=maximal. N=Normal. y=yellow. g=greenish.

Increase in Immature C Neutrophiles	Increase in Old Neutrophiles C	Promyelocytes and Myeloblasts D	Large Lymphocytes D	Lymphoblasts D	Blood in Stool on A Meat-free Diet	Ova in Stool B	Achlorhydria % of B Cases Having	Age Incidence A	Sore Tongue B	Pallor A	Weakness A	Splenomegaly B	Spinal Cord Involvement C	Therapy	Remarks
0	0	0	0	0	0	0	<10	>16	0	0	0	0	0		Satisfactory normals for earlier age groups are not yet available.
0	0	0	0	0	0	0	<10	>14	0	0	0	0	0		Satisfactory normals for earlier age groups are not yet available.
+ to 3+	0	0 to +	0	0	0	0	<10		0	0 to 4+	+ to 4+	0	0	Transfusion or intravenous acacia solution. Stop bleeding.	Most common causes are ectopic pregnancy, ruptured viscus, wounds, operative procedures.
+ to 3+	0	0 to +	0	0	0 to 4+	0	<10		0	0 to 4+	+ to 4+	0	0	Transfusion or intravenous acacia solution. Stop bleeding.	Most common causes are wounds, peptic ulcer, or pulmonary T. B.
0 to 2+	0	0	0	0	0	0	<10		0	0 to 3+ y	+ to 4+	+ to 4+	0	Quinine, plasmochin.	Parasites demonstrable in blood smears. Monocytes increased.
*	0	0	0	0	0	0	<20		0	2+ to 4+	*	0	0	Sunshine or ultraviolet light.	Common in persons who spend much time indoors.
0 to 2+	0 to +	0	0	0	0 to 2+	0 to 4+	<25		0 to +	0 to 3+	0 to 3+	0 to +	0	Anthelmintics, sanitation, iron.	The lower indices occur in hookworm disease and amebic dysentery (chronic hemorrhage).
0 to 3+	0	0 to +	0	0	0	0	>30		0	0	0 to 3+	0 to +	0	Splenectomy in severe cases.	Occurs only in negro race. Sharp pointed elongated or crescentic cells increasing on standing in moist chamber most characteristic.
3+ to 4+	0	+ to 4+	0	0	0 to +	0	<20		0	0 to 4+	0 to 4+	2+ to 4+	0	Roentgen-ray, radium, palliative only.	Platelets often high.
0 to +	0	0 to +	0 to 4+	0 to 4+	0 to +	0	<20		0	0 to 4+	0 to 4+	0 to 3+	0	Roentgen-ray, radium, palliative only.	Large lymphocytes and lymphoblasts chiefly in the acute form. Platelets often low.
0 to 2+	0 to +	0 to +	0 to +	0	0 to 2+	0	<20	<50	0	0 to 3+	0 to 4+	0 to 3+	0 to 4+	Roentgen-ray, radium, palliative only.	Spinal cord involvement when it occurs is partial or complete transverse myelitis.
0 to 2+	0 to +	0 to +	0 to 3+	0 to 2+	0 to 2+	0	<30	>35	0	0 to 3+	0 to 4+	0 to 3+	0 to 4+	Roentgen-ray, radium, palliative only.	Spinal cord involvement when it occurs is partial or complete transverse myelitis.
0 to 2+	0 to 2+	0	0	0	+ to 3+	0	<30		0 to 4+	0 to 3+	0 to 4+	0	0 to +	See paper by Aub.[9]	Dark line on gums, basophilic stippling, impaired renal function, and gastrointestinal symptoms usually also present.
0 to 3+	0	0	0	0	0	0	<10		0	0 to 3+	0 to 4+	0	0	Remove cause of poisoning.	Snake venom, phenylhydrazine, etc., are included in this group.
0	0	0	0	0	0	0	<30		0	0 to 3+	0 to 3+	0	0	Desiccated thyroid q.s. to keep the basal metabolic rate normal.	Basal metabolic rate is less than minus 15.
0 to 2+	0	0	0	0	0	0	<30		*	0	3+ to 4+	0	0	Cortin.[10]	Anemia is present in less than 50 per cent of cases. Low blood pressure. Bronzed skin.
0	3+ to 4+	0	0	0	0 to 4+	0	*	<35	0 to 4+	+ to 4+	2+ to 4+	0	0	Remove cause. Transfusion.	Includes poisoning with benzol, organic arsenicals, and radioactive substances.
0 to 2+	0	0	0	0	0	0	<10	<35	0	0 to 2+ y	0 to +	+ to 3+	0	Splenectomy.	Microcytosis is suggested by the red cell diameter.
+ to 3+	+ to 4+	0 to +	0	0	0 to 2+	0	100	>35	0 to 4+	+ to 4+ y	0 to 4+	0 to 2+	0 to 4+	Diet rich in nuclear material (liver).	Higher reticulocyte counts only at onset of spontaneous or induced remission.
0 to +	0 to +	0	0	0	0 to 2+	*	<50		0 to 4+	0 to 3+	0 to 4+	*	*	Diet (liver).	See infection for equally common anemia picture in sprue.
0 to +	0 to +	0	0	0	0 to +	0 to 4+	<30		0 to 3+	0 to 4+	0 to 4+	*	*	Anthelmintics, sanitation, (liver).	Only 1 in 1000 patients harboring the worm has this picture. 90 per cent have no anemia; remainder as in 5 above.
0 to 2+	0 to +	0	0	0	0	0	<20	<45	0 to 3+	0 to 4+	0 to 4+	*	*	(Liver). Transfusion. Terminate pregnancy.	Do not confuse with common anemias complicating pregnancy, similar to *21*, *23*, *1*, *2*, etc.
0 to +	+ to 3+	0	0	0	0 to 4+	0	>30		0 to 3+	0 to 4+	0 to 4+	0	0	Remove cause of bleeding. Iron.	Common causes are carcinoma or ulceration in digestive or urinary tracts, hemorrhoids, and uterine bleeding.
0 to +	+ to 3+	0	0	0	0	0	<30		0 to 2+	0 to 4+	0 to 4+	0	0	Diet. Iron. Liver.	Food faddists, children or peptic ulcer patients on exclusive milk diet.
0	0	0	0	0	0	0	<5	<25	0	0 to 2+ g	+ to 3+	0 to +	0	Iron	
*	*	*	*	*	*	*	*		*	*	*	*	*	Removal of infection. Transfusion. Specific.	Blood culture is important. Each case must be separately evaluated to determine the relative importance of bone marrow depression and internal blood destruction.
*	*	*	*	*	*	*	>30	>35	0 to 4+	0 to 3+	0 to 4+	0	0	Operative removal. Roentgen-ray, radium.	Anemia is relatively uncommon in this group, but very common in ulcerated malignant tumors.
0	0 to 2+	0	0	0	0 to 3+	0	<30	>30	0	0 to 3+ y	0 to 4+	+ to 3+	0	Low protein diet.	Laennec's cirrhosis is by far the commonest type.
0	+ to 3+	0	0	0	0 to 4+	0	<20	<30	0	0 to 4+	0 to 4+	0 to 4+	0	Splenectomy after transfusion.	Thrombosis of the splenic vein gives an almost identical picture.
0 to 2+	+ to 2+	0	0	0	0 to 3+	0	<20	<40	0	0 to 3+	0 to 4+	2+ to 4+	0	Splenectomy after transfusion.	

a journal article. Therefore, we have grouped, in the table, the chief diagnostic points in the more important clinical conditions in which the differential diagnosis of anemia arises. The figures* given in the table are based in part on our own experience and in part on a study of the literature. This literature is so extensive that space limitations prevent reference to all the articles consulted. Many of them will be found in the bibliographies given by Ordway and Gorham,[6] but our files contain many articles on anemia and related subjects which they have not included.

The plan of the table is as follows: At the top are listed the data which it is most important to secure in differentiating anemias. Those tests followed by the letter A should be determined in every case in which anemia is considered. Those followed by B should be determined in almost every case. Those followed by C are less frequently of value and may be omitted except in the more puzzling cases; while those followed by D are still less frequently of aid in the differential diagnosis. Still other tests, such as cultures, platelet counts, and determinations of coagulation time, bleeding time and clot retraction time, will occasionally be desirable. The numbers in the first column are simply for reference. The second column starts with normal men[7] and women,[8] the findings in whom serve as a basis for comparison. These are followed by twenty-eight conditions which must be considered when studying a patient thought to have anemia. This list could doubtless be extended, but includes the more important conditions. Note that the first sixteen are all characterized, as a rule, by color, volume and saturation indices within the normal range. The next group (17 to 20, inclusive) are sharply differentiated from the others by the high color and volume indices with normal saturation indices. The third group (21 to 23, inclusive) are characterized by a marked tendency toward a decrease in all three of these indices, and this is the only group in which a low saturation index occurs. The final group (24 to 28, inclusive) often have normal indices, but may show low color and volume indices. The numbers in the column headed "Relative Frequency" are in the approximate order of decreasing incidence, i. e., the conditions numbered 1 to 10 are very common, 11 to 20 are less common, and those above 21 are rare. In the remaining columns, an effort has been made to give, whenever possible, actual figures which will include approximately 95 per cent of the cases of each condition. The usual finding in a particular condition will, therefore, be intermediate between the extremes recorded.

In the column headed "Therapy," only the most specifically beneficial treatment is indicated and this in the briefest possible form. Thus "liver" is meant to include not only liver itself, but liver extracts, desiccated stomach, and all nuclear material which has been shown[11,12,13] to be effective in produc-

*An improved method of reticulocyte staining[14] has been developed since the manuscript was submitted for publication. With this method the normal values are from 0.5 to 5.0 per cent, with an average of 1.5 per cent, and the average counts in the anemias will be about three times as great as would be inferred from the figures in the table.

ing a specific reticulocyte increase in patients with pernicious anemia. Similarly, "iron" refers not only to therapy with inorganic iron in large doses, but to therapy with all the known hemoglobin and stroma-building substances.[2] The large variety shown in this list of most important therapeutic procedures demonstrates incontestably the extreme importance of accurately determining the cause of any anemic condition. To merely prescribe a little iron and arsenic because the patient is thought to have a "secondary" anemia, in the present state of our knowledge, borders on criminal malpractice, for the anemia may be due to a readily removable cause (intestinal parasites, chronic lead poisoning, focal infection, bleeding hemorrhoids, etc.). To give "liver" therapy to such cases without an effort to determine and to remove the cause is equally undesirable. Accurate diagnosis is absolutely essential to adequate therapy.

The remainder of the table is largely self-explanatory, but a few points require comment. Obviously, the list of causes of acute and chronic hemorrhage and dietary deficiency anemias is very incomplete, while the individual subdivisions of the intestinal parasite, poisoning and infectious type anemias are not given. They should, however, readily suggest themselves to any well-trained physician. Note that the essential difference between acute internal and external hemorrhage is that, in the former, evidences of internal blood destruction appear within a few days, i.e., increase in the icterus index and in urobilinogen excretion. This may aid as well in differentiating cerebral hemorrhage from thrombosis or embolism, in differentiating hemorrhage from shock, ruptured ectopic pregnancy from most other acute conditions, and in detecting hemorrhagic infarcts, etc.

Note that in sickle cell anemia there are evidences both of rapid red cell destruction within the body and of rapid red cell regeneration, suggesting the possibility that the peculiarly shaped cells are especially susceptible to normal erythrocyte-destroying mechanisms.

Other myelophthisic anemias (malignant tumors involving the bone marrow, osteomyelitis, etc.) show findings similar to those in myelogenous leukemia with the exception that the white cell count in these conditions seldom exceeds 50,000 and the numbers of promyelocytes and myeloblasts tend to be less. Roentgenograms of the bones will usually decide the diagnosis. In each of these conditions, it is probable that a high color and volume index may occasionally occur, but the vast majority show normal indices.

Observe that the aplastic anemia picture is entirely different from that of pernicious anemia, and that there is no reason for confusing them, if the cases are properly studied. In aplastic anemia, the evidences of internal blood destruction are absent until internal hemorrhages occur.

Hemolytic icterus (familial or acquired) is the only group in which the fragility test is of prime importance. Note the almost constant decreased resistance of the red cells and increase in the reticulocyte count. Probably erythrocyte destruction and regeneration do not proceed at so rapid a rate in any other disease. It is, also, the only disease in which the volume index does not give the same informa-

tion as is derived from the determination of the average erythrocyte diameter. Hence, both determinations should be made whenever this disease is suspected.

Observe how sharply the pernicious group of anemias (17 to 20, with an occasional case of myelophthisic anemia, 7) are separated from all other types by the high color and volume indices. Since pernicious anemia itself is relatively common and all other members of the group are uncommon, such cases should be considered as pernicious anemia until proved otherwise. Note that a high color or volume index constitutes almost a specific indication for "liver" therapy.

It is important to keep in mind the fact that the pernicious anemia of pregnancy is rare, while other types of anemia are common in pregnancy. These have not been listed under a separate heading because it seems to the authors that most of the true anemias (disregarding the 10 to 20 per cent relative decrease in erythrocytes due to increased plasma volume in the last months) occurring in pregnancy can be placed in one of the other groups. It must not be forgotten that pregnant women are subject to most of the disease conditions to which non-pregnant women in a similar age group are susceptible and that they are hypersusceptible to some of them. It is probably true that due to the demands of the fetus for iron and other erythrocyte-building materials in the latter months of pregnancy, an anemia might develop on a dietary intake which would prove adequate for a non-pregnant woman; but the fact remains that this is a dietary deficiency anemia, giving rise to the same signs and symptoms and responding to the same therapy as in the non-pregnant woman. The tendency in pregnancy to pyelitis, nephritis, and other infections usually giving rise to anemia is well known.

Observe that most cases in the next group of conditions (21 to 23) are distinguished from all other types of anemia by the low saturation index. Low color and volume indices occur more commonly in these than in other conditions. Since, of these conditions, chronic hemorrhage alone is common, it seems justifiable to consider this as the most probable cause of an anemia in which the saturation index is below 0.85, until otherwise proved. Note that a low saturation index constitutes a specific indication for "iron" therapy and that administration of erythrocyte- and hemoglobin-building material may be expected to be of benefit in any anemia in which the color or volume index is low, while in other anemias such therapy is of very doubtful value.

The final group of anemias (24 to 28 inclusive) can be separated from group I only in the cases in which the color and volume indices are low. As a cause of anemia only the infection group is very common, for malignant tumors, in which ulceration (with secondary infection or hemorrhage) and bone metastases can be excluded, seldom cause anemia.

The most common cause of anemia is unquestionably infection. The mechanisms of the production of anemia in infection are probably chiefly bone marrow depression and internal blood destruction. In most infections, the evidence suggests that the former factor plays the predominating rôle. But in infections with organisms producing

a hemolytic toxin, the latter factor predominates. Unquestionably, the nature of the anemia varies with the type and virulence of the organism, with the location and extent of the infection, and with the condition of the hematopoietic system of the individual. It is probable that almost every infection, whether acute or chronic, has some anemia-producing tendency. This accounts for the fact that the so-called "normal figures" for hemoglobin and red cell count based on studies of hospital or dispensary patients who do not have the commonly recognized causes of anemia are consistently lower than figures based on studies of perfectly healthy persons.

Note that many of these conditions may co-exist with red cell counts and hemoglobin estimations within normal limits, that in myelogenous leukemia an actual erythrocytosis sometimes occurs, and that the lower limits of the counts and hemoglobin estimations are very variable in the different conditions. We have studied the blood of many pernicious anemia patients within a few hours of death and find the red cell counts usually between 400,000 and 800,000 and the hemoglobin between 1.5 and 3.0 gm. per 100 c.c. We feel certain that these figures represent the lower limits compatible with life. Hence, the figures of 143,000 reported by Quincke and of 138,000 reported by Naegeli were probably due to errors in technic.

The reader may make many other deductions from a study of the table. In individual cases, it must not be forgotten that two or more of these conditions may co-exist.

It is obvious that any theory of the etiology of pernicious anemia must explain the relationship to achlorhydria, the evidences of increased rate of red cell formation and red cell destruction, the large size of the circulating red cell, the occurrence of similar blood pictures in some cases of sprue and pregnancy, and the therapeutic value of liver, kidney, stomach, nucleated red cells and extracts of these tissues. The common factor in the effective therapeutic material would seem to be relative richness in nuclei. An hypothesis which might explain this syndrome is the following: In the nuclei of most mammalian organs and tissues there exists a substance which is necessary for the development of mature erythrocytes of normal size and resistance to the wear and tear of circulation and to the normal mechanisms for the destruction of red cells. The normal gastric secretion is capable of liberating this substance from skeletal muscle (meat) and other sources. In the common form of pernicious anemia, there is associated with the achlorhydria a deficiency of the digestive activity which liberates this effective substance. A deficient supply of this substance results in the formation of large cells by the bone marrow which are destroyed with exceptional readiness in the blood stream. This rapid destruction leads to the increased icterus index, to the increased excretion of urobilinogen in stools and urine, to the increased stores of iron in the liver and the spleen with resultant enlargement of these organs, and to the anemia. The anemia serves as a stimulus to more rapid red cell regeneration, giving rise to the tendency for nucleated, polychromatophilic and reticulated red cells to appear in the blood stream in increased numbers.

thus completing the hematologic picture of this disease. Organs rich in nuclei contain enough of this substance (probably not nucleoprotein or nucleic acid, but either a digestion product of these substances or something associated with them in the nucleus) in readily available form so that ingestion in large amounts gives an adequate supply even in the absence of the digestive substance. In sprue, the failure is probably in absorption (due to diarrhea) of the substance after liberation by digestion, while in the pernicious anemia of pregnancy, it is possible that there is a relatively insufficient intake of the substance to supply the needs of both the mother and the fetus.

Summary

A table showing the results of the most important examinations in the different types of anemia is given, together with a discussion of the fundamental causes of anemias and the differential diagnosis of clinical anemias. A theory of the etiology of pernicious anemia is advanced.

Conclusions

1. The term "secondary anemia" should be discarded as it is not sufficiently descriptive and anemias formerly grouped together under this term differ widely in etiology, symptomatology, blood findings, and in response to different types of therapy.

2. An accurate diagnosis of the etiology is essential to the proper treatment of anemias. To facilitate this differential diagnosis, a table is presented which gives the more important laboratory and clinical findings with the chief therapeutic indications in twenty-eight of the more important conditions which may cause or be confused with anemia.

3. A cause for anemia may exist without the development of actual anemia, since it is possible for blood regeneration to keep pace with blood destruction or with hemorrhage.

4. There are only three fundamental causes of anemia, i.e., deficient formation of red cells or hemoglobin, excessive destruction of red cells or hemoglobin within the body, and loss of red cells and hemoglobin from the body. These deserve more thorough study than they have previously received.

5. Clinical anemias should be studied with the object of determining what is the relative part played by each of these fundamental factors in any individual case. Criteria to use in this evaluation are indicated in this paper.

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A Comparative Study of the Use of Whole Liver, Liver Extract and Ventriculin*†

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THE use of various anti-anemic substances in the treatment of primary anemia is now well recognized and established in medical therapeutics. Although sporadic cases have appeared in the literature in which some form of liver therapy has failed, there is abundant evidence which demonstrates the undoubted value of anti-anemic substances. As to their comparative value, however, there is relatively little to be found which indicates any difference in response to them. Thus, Minot and his co-workers[1] report that they noted no difference in the reticulocyte response obtained in the feeding of either whole liver or liver extract. Ordway and Gorham[2] treated nineteen cases with liver and six with liver extract, and from their study concluded that both groups responded equally well. Davidson et al.[3] arrived at a similar conclusion. In a discussion on the use of "Desiccated Stomach" in the treatment of pernicious anemia, Isaacs and Sturgis[4] stated that they were unable to find a difference in the course of the remission, or in the response of the neurologic lesions, with ventriculin therapy as compared to that found with the use of liver. Conner[5] was also of the opinion that the results of treatment with "swine stomach" would compare favorably with those derived from the use of liver or liver extract.

Quite in contrast to the above studies are those of Schulten[6] and Berglund et al.[7], in which no hemopoietic response with liver extract was found, but in which a definite remission resulted with the use of fresh whole liver. The case study reported herein bears a striking resemblance to the above group except that in addition to the whole liver and liver extract used above, ventriculin (Parke, Davis & Company) was also among the preparations administered.

The patient under discussion had been under our observation on two previous occasions, and at both times was successfully treated with liver extract. At the time of his third admission to the hospital, he was in a state of relapse with a marked anemia. The administration of ventriculin, and later the use of liver extract, failed to produce any significant remission in the blood picture. It was not until the patient was given the juice of whole liver that a satisfactory erythropoietic

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†Received for publication, September 17, 1931.

response on the part of the bone marrow was obtained. Because of the rarity of such a comparative study in the same individual, and because of the unusual nature of the results obtained, it was thought advisable to report the case study in the hope that it might offer some aid in the treatment of those cases which appear refractory to the usual anti-anemic therapy.

Case Summary

First Observation. The patient, O. B., male, aged 20, was first seen on the medical service in March, 1929. At the time of his first admission he complained of weakness, loss of weight, sore tongue and paresthesias of the hands and feet. Examination at that time revealed an emaciated, pasty appearing boy with a ptosis of the left eyelid, a corneal scar in the left eye and an atrophy of the tongue. The heart was negative except for an apical systolic murmur. The spleen was enlarged to about two fingerbreadths below the costal margin and was firm and tender. There were no objective neurological findings.

The blood picture was that of a primary anemia with hemoglobin, 65 per cent; red blood cells, 1,710,000; white blood cells, 9,150. The differential count revealed 76 per cent polymorphonuclears; 16 per cent lymphocytes, and 8 per cent mononuclears. Red cells showed anisocytosis and poikilocytosis. Gastric contents showed no free hydrochloric acid. The indirect Van den Bergh was slightly positive.

On the basis of the above findings a diagnosis of pernicious anemia was made and liver extract therapy instituted (vials IV—daily, equivalent to 400 gms. fresh raw liver). As a result of this treatment the patient had a prompt, though comparatively small, reticulocyte response (5.6 per cent) and a very definite increase in the percentage of hemoglobin and in the number of red blood cells. Five weeks after the institution of the liver extract therapy, the hemoglobin rose to 85 per cent and the total red count became 4,000,000. Coincident with the remission in the blood picture, the patient gained weight and his symptoms disappeared.

During the following ten months he remained symptom free on one quarter pound of liver a day with occasional substitution of liver extract. At the end of this time, he became unable to purchase liver and as a result some of his former symptoms returned. His blood picture, however, remained normal. (Abortive relapse of Isaacs.[8])

Second Observation. During the second period of observation there was little in the general physical and laboratory findings which differed from those present at the time of the patient's discharge from the hospital ten months previously. After only a brief period of hospitalization his symptoms disappeared and he was again discharged on one vial of liver extract, three times daily.

For the following six months the patient continued on liver extract and remained in perfect health. At the end of this time, however, he became financially unable to purchase liver extract, and as a result he took no anti-anemic substance. During this time he lost weight, became weak and developed numbness and tingling of the hands and feet. In addition to this, he complained of nausea and vomiting. With these symptoms he re-entered the hospital.

Third Observation. Physical examination on his third entrance to the hospital revealed little that was not found at the time of his first admission. There was obvious pallor and evidence of considerable weight loss. The ocular findings were as before and the atrophy of the tongue was still in evidence. The spleen was enlarged to the same extent as formerly but appeared to be less tender to palpation. There was no disturbance in the vibratory, or motion and position senses in the extremities. Reflexes were normal. Heart and lungs were negative.

Laboratory Data. Blood count: Hemoglobin, 50 per cent; red blood cells, 2,500,000; color index, 1.1; white blood cells, 4,000; polymorphonuclears, 39 per cent; lymphocytes, 60 per cent; eosinophils, 1 per cent. Red cells showed poikilocytosis, anisocytosis and polychromatophilia. Diameter of red cells varied between 9.5 and 4

μ. Reticulocytes, 0.4 per cent. Blood fragility, beginning hemolysis, 0.4 per cent; complete 0.3 per cent. Hematocrit study: volume percentage of RBC = 29. Blood culture and blood Wassermann, negative. Blood nitrogen, 28.6 mgs. Blood sugar, 0.100 per cent. Blood cholesterol, 143 mgs. Blood platelets, 383,000. Bleeding time, four minutes. Coagulation time, four and one-half minutes. Van den Bergh, direct and indirect, negative. Gastric analysis (with histamine), no free hydrochloric acid (three examinations). Urinalysis, negative. Urobilinogen, positive. Stool analysis, normally formed; no blood, ova or parasites. X-ray examination: gastro-intestinal, negative; chest, negative except for extensive root deposit with exaggerated trunk markings throughout both lung fields.

Clinical Course

First Period. During the first eighteen days of hospitalization the patient was given ventriculin (Parke, Davis & Company), the initial dose consisting of three vials daily, (30 gms.). At the end of ten days the dose was increased to four vials, this being continued for eight days. Because of persistent nausea and vomiting, an attempt was made to give this preparation by rectum (Vials VI, 60 gms), but this was unsatisfactory.

During the period of ventriculin therapy there was no clinical improvement. The nausea and weakness persisted. The blood picture showed no appreciable change, the reticulocytes increasing to 0.9 per cent and the total red count reaching its highest peak of 2,500,000 on the tenth day, this representing a total gain of only 250,000 red cells. The hemoglobin dropped from the original 50 per cent to 38 per cent on the eighteenth day. The white count remained low throughout; the differential showing a constant lymphocytosis, on one occasion reaching 86 per cent. The polymorphonuclear cells showed an almost constant shift to the left. While the total blood count showed little or no change, a study of the blood smear revealed evidence of attempts at blood regeneration, i.e., stippling of red blood cells, normoblasts, etc.

Throughout the entire period of ventriculin therapy the patient had a daily temperature elevation varying from 99 to 100. Careful and repeated urinalyses, sinus and chest x-rays, etc., failed to reveal any evidence of infection or other cause for this febrile reaction.

Second Period. During the second period the patient was given liver extract (Lilly's No. 343, one vial = 100 gms. whole liver) starting with four vials a day and after two weeks increasing this to six vials daily. The latter dosage was given for one week. While under this therapy the blood picture showed little change. The reticulocytes rose from 0.3 per cent at the beginning of the period to a maximum of 11.4 per cent on the eleventh day. The red cell count increased from 1,230,000 to 2,020,000 on the sixth day, and then fell to 1,895,000. The hemoglobin increased from 38 to 48 per cent over the entire period of three weeks. The leucocytes remained low throughout, only on one occasion reaching as high as 8,100. The blood smear showed evidence of blood regeneration with a tendency to a right shift of the leukemoid picture. Throughout this period also, the patient continued to have an unexplained daily temperature elevation, although the general level was below that of the preceding period. The general condition showed no appreciable improvement.

Third Period. Following the unsuccessful use of liver extract, first of three and then of six vials a day, the patient was next given the juice of one pound of whole liver daily. The following day the reticulocyte count rose from 0.33 per cent to 0.5 per cent and on the third day it rose to 9 per cent. The red count increased from 1,900,000 to 3,000,000 on the eighth day, the leucocyte and differential count remaining practically normal throughout. The smear showed evidence of progressive blood regeneration.

On the fifteenth day of "liver juice therapy" it became obvious that the patient had reached a standstill in his blood picture. The hemoglobin had attained a level of 78 per cent and the red count had already started to drop slightly. The juice of three pounds of liver was then given daily with a resulting progressive increase in the hemoglobin and red count. On the seventh day the hemoglobin rose to 92 per cent and the red count reached 4,720,000. The rest

of the blood count was normal—the smear presenting a normal blood picture.

Coincident with the elevation in the blood count there occurred a distinct improvement in the clinical condition. Appetite became progressively better, nausea and vomiting ceased, and strength returned. The temperature elevation persisted.

An attempt to decrease the dose of liver juice to that of two pounds daily, resulted in a prompt drop in the blood count and a recurrence of a characteristic group of symptoms, viz., numbness and tingling of fingers and stiffness of the neck. This picture was seen on several subsequent occasions during a relapse in the blood picture. Because of this the dose was increased to its former level with a resulting prompt improvement in the blood picture and in the clinical condition of the patient.

Realizing the impracticability of taking whole liver juice after leaving the hospital it was thought advisable to try some preparation which would be more conveniently used by the patient. Although liver extract had previously failed it was tried again hoping that it would maintain the blood level produced by the whole liver. The use of three vials a day was promptly found to be inadequate, and the dose was therefore increased to six vials. This resulted in a prompt return of the blood picture to its former level. Two weeks later it became necessary to increase this to eight vials daily because of a drop in the blood count and a return of the above described symptoms so characteristic in this case of a falling blood picture. This proved to be adequate for only two weeks, and at the end of this time the clinical condition of the patient again started to fail. Because of this the liver extract was supplemented by whole liver (one-third pound daily), this resulting in prompt improvement in the general condition. After one month on this "combined therapy" the liver was omitted from the diet entirely. Ten days later the amount of liver extract was decreased to six vials without any change in the blood picture or in the clinical condition of the patient. At the present writing this dosage has been further reduced to three vials a day. The blood count at present is: hemoglobin, 97 per cent; red blood cells, 5,120,000 (on three vials a day for two weeks).

[It has subsequently come to our attention that this patient had another relapse during which he was cared for in the Simpson Memorial Institute for Medical Research, Ann Arbor, Michigan. While in this institution he was successfully treated with intravenous liver extract after the use of stomach and liver preparations by mouth had failed.]

Comment

In a review of the above case study several facts are worthy of note. One is impressed with the successful use of whole liver after both liver extract and ventriculin failed. There is also noted the necessity for large and increasing doses of anti-anemic substances in order to obtain the desired blood level.

The first observation is of particular interest in this case when it is recalled that the patient under consideration had previously responded well to three vials of liver extract a day, and even at the present time is satisfactorily controlled on similar quantities of the same preparation. In the absence of complicating factors such as infection, etc., it is thought that such a variation in response at different periods can best be explained on the basis of a different reactive state of the bone marrow during the various remissions.

The reason for the success of whole liver in this case after the other products had failed is not at once apparent although several explanations suggest themselves. One might first question the potency of the products used. The ventriculin was supplied by the manufacturers, Parke, Davis & Company, for experimental purposes. The liver extract used was the standard

product of Eli Lilly & Company (No. 343).

A second explanation lies in the possibility of an inadequate dosage of these products. Unfortunately, the administration of larger quantities of ventriculin was prevented by the patient's persistent nausea and vomiting. Final conclusion, therefore, should not be drawn regarding the efficacy of this product in this case since only the minimum amount could be used. It will be noted, however, that the usually required dosage was administered without success. A significant elevation of the reticulocyte count did not occur. With liver extract, although a definite reticulocytosis was produced, the administration of nearly twice the quantity ordinarily required was insufficient to produce any appreciable increase in the red blood cell count. In contrast to this, the use of proportionately less fresh whole beef liver as liver juice, was sufficient to produce not only the same reticulocyte response as that resulting from liver extract, but a definite elevation of the total red count and percentage of hemoglobin as well.

A third explanation, i.e., the presence of an infection, is suggested by the persistent fever and the "left shift" of the neutrophilic elements of the blood. That an infection may alter the response of the blood forming organs to anti-anemic substances is illustrated in the recent case report of Smithburn and Zerfos[9]. In an earlier publication by Minot, Murphy and Stetson[1], the depressant action of infections on bone marrow was also emphasized. In this case, as already stated, no focus of infection could be found. Of further importance in this connection is the fact that the fever was not confined to the period of ventriculin and liver extract therapy, but continued throughout the administration of whole liver juice as well.

The failure of the above suggestions to account for the results in this case, leads one to suspect that the explanation may lie in the composition of the whole liver in contrast to that of liver extract or ventriculin. The question, therefore, arises—does whole liver contain some principle not present in either of the other two substances, or present in lesser quantity, which renders it more effective in its action on the hemopoietic system when the latter is in a state of marked depletion? That some difference does exist between the effect of these various substances on blood forming tissue is suggested by the eosinophilia resulting from the use of whole liver in contrast to the absence of this response with the use of liver extract. (Meulengracht and Holm[10] and others[11,12]. The absence of this effect with ventriculin has also been noted (Goldhamer[13])). Likewise, the special effect of whole liver on hemoglobin formation as compared to that resulting from the use of liver extract is further evidence of the difference of effect of these substances. (Isaacs, Sturgis and Smith,[14] and others[15]). To explain a variation in erythrocytic response on the same basis is, of course, conjectural, but would nevertheless appear worthy of consideration.

The second observation mentioned above in which it was noted that larger quantities of anti-anemic substances were required for adequate stimulation of the bone marrow has already been noted by others. Thus

Minot and his co-workers[1] were able to produce a secondary reticulocyte response together with a marked increase in the total red cell count after feeding larger quantities of liver pulp. In our case there developed a secondary reticulocyte response immediately upon the administration of fresh whole liver juice and simultaneously with this, a definite elevation in the total red count and percentage of hemoglobin. Further increase in the amount of liver was then required to attain the maximum blood level desired. As already stated in the discussion of the case early attempts at decreasing the quantity of whole liver as well as substituting liver extract for the latter were unsucessful in maintaining the desired blood picture. It was not until two and one-half months after the institution of liver therapy that substitution by liver extract became possible. Such an observation as this, in the absence of complicating factors, would lead one to postulate that the response of the bone marrow in some cases, and at certain periods, is dependent upon the "quantity" of the anti-anemic substance administered as well as the "quality" as already discussed above.

Summary

A case of primary anemia is presented which failed to respond to both ventriculin and liver extract, but which later responded satisfactorily to the juice of whole liver.

Attention is also drawn to the fact, that larger and increasing doses of anti-anemic substance were required to produce and maintain the desired blood level.

It is suggested that in those cases which prove resistant to the usual "anti-anemic extracts", whole liver be given a trial. It is further suggested that large quantities of the anti-anemic substance be given before the case be considered refractory.

We wish to thank Mr. Emil Schleicher of Parke, Davis and Company, for his technical and material assistance in the study of this case.

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If You Have a Persistently High Blood Pressure

"IF YOU have passed the milestone of middle life, you should develop a hobby of some type, which is interesting, pleasant, and not a part of your daily employment or thought. Secondly, you should teach an understudy, if you are in business, to take charge of your affairs from time to time, so that when that day comes when you should play a less active rôle in the management of your affairs than formerly, it will lessen that inevitable anxiety which will confront you when you realize that your endurance and physical fitness are becoming less.

"Finally, if you represent that large group of despondents who have high blood-pressure disturbances as a part of their general body let-down, allow me to say a word of cheer. If your body were a mechanical thing, manipulated by a motor, with bearings and joints that were dependent upon protection, adjustment, and lubrication in a manner similar to that of the automobile, and if life's journey were traveled along a rough and rugged road which ended in precipitate heights, and you wished to reach life's goal of matured years, you could do any one of the following three things: Lighten your daily loads, protect the wear and tear of your machinery, or smooth out the roadbed."

(From *How's Your Blood Pressure?* by Clarence L. Andrews, M.D., F.A.C.P., The Macmillan Company, 1931.)

Raynaud's Disease Affecting Men*†

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Of the vasospastic disorders affecting the peripheral circulation, of which Raynaud's disease represents the most typical form, the distribution by sex is the reverse of that found in organic disease of the peripheral arteries.[2] Various writers have given the incidence of Raynaud's disease in the female as from 60 to 90 per cent, and a critical survey of the reports of cases offered as examples of Raynaud's disease in the male has given evidence of an exceedingly high proportion of erroneous diagnoses.[1] Many such cases represented classical examples of thrombo-angiitis obliterans.

The criteria for diagnosis of Raynaud's disease are as follows: (1) episodes of change in color, of the vasospastic type, excited by cold or emotion; (2) bilaterality; (3) presence of normal pulsations in the palpable arteries; (4) absence of gangrene, or its limitation to minimal grades of cutaneous gangrene; (5) absence of any primary disease which might be causal, such as cervical rib or organic disease of the nervous system, and (6) symptoms of two years or of longer duration.

The first four criteria were succinctly stated by Raynaud.[1] The fifth and sixth have been added by us to emphasize the necessity of eliminating causes to which the vasomotor symptoms might be secondary.

Present Study

A diagnosis of Raynaud's disease, uncomplicated by scleroderma or trophic changes, and unassociated with arthritis, has been made in 150 cases at The Mayo Clinic. The characteristic symptoms of vasomotor episodes of discoloration of the skin of the fingers or toes, occurring bilaterally and intermittently, were present in every instance. Males comprised seventeen of these 150 cases (12 per cent), but in only seven of these seventeen (5 per cent of 150) could the diagnosis be substantiated on the basis of additional requirements of long duration of symptoms and of demonstration of absence of such conditions as cervical rib, and organic disease of the peripheral arterial system.

In each of the remaining ten cases (table) the diagnosis "probable Raynaud's disease" was made; in each instance some objection could be offered to the diagnosis of true Raynaud's disease. These objections are as follows: in cases 1 and 8 the duration of symptoms was only four and

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†Submitted for publication, December 9, 1931.

six months, respectively; in case 2, rudimentary cervical rib was demonstrated roentgenologically although it probably was not of significance; in cases 3, 4, 5, 6, 7, 8, 9, and 10, specific notation as to presence of pulsation was lacking, and in case 6, there was no notation as to the duration of symptoms. Gross evidence of obstructive arterial disease was not present in any of the cases. However, in those cases in which there was no specific mention of pulsations in the peripheral arteries, the possibility of the presence of arterial disease characterized by occlusion cannot be excluded.

In seven of the seventeen cases (41 per cent) there was evidence of functional or neurotic disturbances, such as dizziness, nervousness, flatulence, vague gastric distress, biologic inferiority, or cardiac neurosis. The incidence of these disturbances exceeds by 17 per cent that found in a group of females with Raynaud's disease.

The ages of sixteen of the patients at the onset of symptoms were as follows: first and second decades of life, eight cases; third decade, three cases; fourth decade, five cases. In the remaining case the age at onset of the symptoms was not known. This emphasizes the fact that Raynaud's disease is a condition of youth and middle age. In a series of 115 females with uncomplicated Raynaud's disease, 77 per cent of the patients manifested their first symptoms before the age of forty years.

Data on height and weight were available in fifteen of the seventeen cases. Comparison with standard tables based on age and height and allowing a variation of plus or minus 10 pounds, disclosed that three of the patients (20 per cent) were overweight; seven (47 per cent) were of normal weight, and five (33 per cent) were underweight. In this small series of cases, such a distribution is probably of no significance. For comparison: among women with Raynaud's disease, the thin, asthenic type of person is more frequently seen; of 112 women, 50 per cent were underweight, 35 per cent of normal weight, and 15 per cent of more than normal weight.

Forty-seven per cent, eight of the seventeen men, were unmarried. For comparison: 40 per cent of 121 women with the same type of Raynaud's disease were unmarried. The comparative youth of a number of the male patients doubtless accounts for their being unmarried.

Comment

A convincing explanation of the low incidence of Raynaud's disease among men, as compared with women, has not been offered. Equally as difficult of explanation is the comparatively high incidence (98 per cent) among men[2] of thrombo-angiitis obliterans. Considerable weight in diagnosis can be given to the predilection of these two diseases for the respective sexes. If a novice in the diagnosis of peripheral vascular diseases were shown 100 women and 100 men known to be affected with either Raynaud's disease or thrombo-angiitis obliterans, he could arrive at the correct diagnosis in 90 per cent of the cases with no further knowledge than that of the sex of the patients. The presence of the other 10 per cent, however, emphasizes the necessity of careful development of the clinical history and of examination with assiduous attention to details.

Our studies have indicated that men

TABLE
SUMMARY OF CASES OF RAYNAUD'S DISEASE AFFECTING MEN

Diagnosis	Case	Age, years	Episodes of discoloration: Region: Fingers	Region: Toes	Duration, years	Type: Pallor	Type: Rubor	Type: Cyanosis	Type: Bilateral
True Raynaud's Disease	1*	24	Yes	Yes	10	Yes	No	Yes	Yes
	2*	48	Yes	Yes	3	Yes	Yes	No	Yes
	3*	49	Yes	Yes	5	Yes	No	No	Yes
	4*	19	Yes	No	4	Yes	No	Yes	Yes
	5*	39	Yes	No	20	Yes	No	No	Yes
	6*	18	Yes	Yes	9	Yes	Yes	No	Yes
	7*	28	Yes	No	12	Yes	Yes	Yes	Yes
Probable Raynaud's Disease	1*	37	No	Yes	0.33	Yes	No	No	Yes
	2*	43	Yes	No	1.5	Yes	No	Yes	Yes
	3**	54	Yes	Yes	10	Yes	No	No	Yes
	4**	40	Yes	No	30	No	No	Yes	Yes
	5**	49	Yes	No	6	Yes	No	No	Yes
	6**	33	Yes	No		Yes	No	No	Yes
	7**	54	Yes	Yes	40	Yes	No	Yes	Yes
	8***	30	Yes	No	0.5	Yes	No	No	Yes
	9**	28	Yes	No	5	Yes	No	Yes	Yes
	10**	26	Yes	No	10	Yes	Yes	Yes	Yes

* Denotes normal pulsations in the radial, ulnar, dorsalis pedis, and posterior tibial arteries.

** Denotes no information regarding pulsation.

*** Denotes normal pulsation in the radial artery and no information regarding pulsation in the ulnar, dorsalis pedis, and posterior tibial arteries.

are particularly subject to organic derangement and women particularly to functional derangement of the peripheral vascular system. Whether this is because men and women live and work at different paces, whether the reason is that women secrete a protective hormone denied to men, or whether the explanation lies in the different tendency of members of the two sexes to acquire diseases of which neurosis is an element is not known.

SUMMARY

The condition of seven men met all the requirements for a diagnosis of Raynaud's disease. In an additional ten cases, the diagnosis was probable Raynaud's disease. Of all patients affected with uncomplicated Raynaud's disease, about 5 per cent were men (seven cases of 150). In an additional 7 per cent of uncomplicated cases, also (ten cases of 150), the patients were men; in this 7 per cent of cases, the diagnosis seemed warranted but some objection could be raised to it. Possible reasons for the predilection of peripheral vascular diseases for one or the other of the two sexes are mentioned in the paper.

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Does Liver Therapy Benefit the Diabetic?*†

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As a consequence of the reports of Blotner and Murphy[1] a number of trials have been made in this hospital with liver therapy for diabetes mellitus. The first of these was made with feeding of whole liver, 180 grams daily, to two cases of clinically unvarying tolerance. The results gave no encouragement at that time (1929). In July, 1930, our attention was directed to the possible merits of a mixture of an extract of horse liver, horse blood, with hypophosphites, alcohol, and saccharin, referred to below as "liver mixture". The manufacturers of a certain commercial horse liver and blood mixture had reports from two clinicians that this preparation had apparently been of marked benefit to some diabetic patients. This mixture has been prepared and marketed for the treatment of anemias other than pernicious anemia. Consequently the manufacturers prepared the special mixture described above, omitting the sugar and glycerol from the usual commercial formula. Late, on request they supplied also simple aqueous liver extracts, preserved with 16 per cent alcohol, and dried residue from aqueous liver extract. Since careful clinical records were not available from the clinicians who had first reported on the ordinary mixture, they were eager to have dependable studies of such products made before any attempt was made to enter into commercial production. These materials were made under the personal supervision of the chemist at the packing plant. The commercial use of meat from the horse has been developed to a large extent by this firm, both for foreign trade and for the production of compounded rations for small animals in this country. The selection of animals and the plant conditions are apparently excellent. This report therefore applies entirely to the use of material from the liver of the horse.

The first patient studied was a 15 year old girl who had been diabetic for four years. She required 105 units of insulin daily with a maintenance diet. An attempt was made to replace insulin with "liver mixture", but a precomatose condition was apparent in 24 hours after insulin withdrawal. A few days later an attempt was made to reduce the insulin dose by substituting the oral preparation for 20 units of insulin. When 85 units were combined with 15 c.c. of "liver mixture" before each meal for one week there was no evidence of benefit. An increase to 30 c.c. three times daily was

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†Received for publication, August 10, 1931.

no better. After a nine day interval a simple aqueous liver extract was tried for seven days without benefit. Thereupon a liver press juice was substituted for six more days. Throughout this period 95 units of insulin were administered daily, in spite of which there was slight ketosis and glycosuria as marked as when insulin was given alone.

At the same time a young man was treated with "liver mixture" as soon as it had been found that on a standard 1525 calorie diet he excreted 14.4 to 16.5 grams of sugar daily. With the use of 30 c.c. of the oral preparation before each meal for three days his glycosuria rose to 23.8 to 27.5 grams, with unabated ketosis. With the use of 30 units of insulin daily he was free from glycosuria and ketosis while using a 2270 calorie diet.

An emaciated diabetic man of 40, weighing 100 pounds, was found to maintain his weight on a 1965 calorie diet. While using 10 units of insulin daily he had only traces of glycosuria, with infrequent positive nitroprusside tests on the urine. Blood sugar values of 187 to 199 mg. per 100 c.c. were observed in the morning. Addition to this routine of "liver mixture" in doses of 15 c.c. three times daily for five days, then of 30 c.c. before each meal for six days, was ineffective. There were no consistent changes in glycosuria, weight, or the level of blood sugar. Ketosis did not occur during the last week of this trial, but it was absent except for three days in the following three weeks when insulin alone was used at the same level as before.

A 57 year old man with dry gangrene of several toes was found to lose 14.7 to 18.2 grams of sugar while on a 1525 calorie diet. There was no ketosis. The use of "liver mixture", 15 c.c. before meals for six days, was followed by an apparent improvement, with glycosuria less than six grams on four of the six days. Use of the simple extract of liver in 15 c.c. doses for five days, in 30 c.c. doses for three days, and of the liver press juice in 30 c.c. doses for five days gave similar results. When only the diet was used as treatment the result was just as good, with glycosuria continuing to vary from 3 to 8 grams daily. During the period of observation the morning blood sugar had dropped from its original level of 200 mg. to 80 mg. six days after stopping liver press juice. The use of insulin in two doses of 5 units each abolished all glycosuria. This case had evidently made the usual improvement in sugar tolerance which must be attributed to dietary restriction alone. The liver treatment cannot be considered responsible for even this slight improvement.

It was considered possible that absorption of some insulin given by mouth might be facilitated by liver materials in a way similar to that claimed by Stephan.[2] Therefore a trial was made by mixing insulin in a solution of the liver and blood extracts only, the materials used for making the "liver mixture". The patient was a male, aged 33, who required 52 units of insulin to remain free from glycosuria and ketonuria on a 2270 diet. When the insulin was given in the tissue extracts by mouth, the dose and time being the same, glycosuria reappeared. The insulin doses were doubled without any benefit. The loss of sugar was similar

during the periods with such therapy and during intervals when only the liver and blood extract were administered, or for two days without therapy. A return to the use of 52 units of insulin promptly restored the balance of the patient. There is no reason to conclude that the insulin given by mouth to this patient had any effect.

Following this series of negative results it was thought best to try an exact duplication of some of the work reported by Blotner and Murphy.[1] An aqueous extract of liver was heated to 80° C., and the precipitated material was dried in an air current of 40° to 50° C. This treatment is said by the above authors to leave the activity of their preparations unaffected. The dry material from one pound of liver was estimated to be 24 grams. The use of 8 grams of this powder with each meal was easily arranged; this should be the equivalent of the ingestion of one pound of liver daily so far as the substances in such a preparation are concerned.

A male patient, aged 23, using 1965 calories and 35 units of insulin had slight morning glycosuria, minimal amounts of acetone in the urine, and his blood sugar was 143 and 140 mg. on two mornings. The use of 24 grams of dried liver powder as above made no change in the urine findings, the blood sugar after two days was 136 mg. in the morning; there were no insulin reactions.

Another patient, aged 14, required the same insulin dose and the same diet, but had no traces of acetone in the urine. In this case the insulin was withheld and the 24 grams daily of liver powder administered. Glycosuria and ketonuria reappeared and the blood sugar rose from 120 mg. to 167 mg. The liver powder was continued and the insulin doses were raised gradually. Not until after two days on the original dose of 35 units was the glycosuria and ketonuria abolished.

Further trials of this powder were made by giving it with the usual breakfast and insulin, following which series of blood samples were taken. On the preceding day a control observation was made. The protocols for two such cases are given in the table. It seemed in patient "M" that the blood sugar was less variable on the morning when the liver powder was given. The advantage is certainly not great. In the case of "A" the difference between the two curves is within the limits of variation commonly seen on successive days.

For the supply of materials as desired and for the cost of hospital study for these cases grateful acknowledgement is made to the Chappel Bros., Inc., of Rockford, Ill. Their chemist, Dr. A. E. Meyer, reports that he had made numerous attempts to detect activity of these and other liver preparations in rabbits, normal dogs, totally and partly depancreatized dogs, but without any convincing evidence of antidiabetic action.

We fail to find evidence that there is antidiabetic activity in the "liver mixture" or in the alcoholic extracts of liver and blood, liver alone, or in a press juice prepared from horse liver. A dried powder of the heat precipitate from aqueous liver extract was tried by methods similar to those used by Blotner and Murphy, but without any favorable result. No explanation is suggested for the failure to confirm the work of these authors, but the re-

sults reported agree with the negative results of dePencier, Soskin, and Best,[3] Soskin, Binswanger, and Strouse,[4] as well as of Root.[5]

TABLE OF BLOOD SUGAR VALUES

PATIENT "M"

TIME, HOURS	BLOOD SUGAR, mg. PER 100 c.c.	
	USUAL DAY	WITH LIVER POWDER, 16 gm.
0	136	125
Insulin, 15 U. Breakfast		
1	97	128
2	175	123
3	117	
4	73	115

PATIENT "A"

TIME, HOURS	BLOOD SUGAR, mg. PER 100 c.c.	
	USUAL DAY	WITH LIVER POWDER, 16 gm.
0	160	179
Insulin, Breakfast		
1	144	163
2	156	162
3	121	123
4	118	108

Breakfast, both days: Protein, 18; Carbohydrate, 17; Fat, 51 grams.

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Primary Sclerosis of the Pulmonary Artery*†

Report of a Case

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ARTERIOSCLEROSIS of the pulmonary artery may be primary or secondary. The primary type is rare and affects the small arteries and the arterioles of the pulmonary circulation with or without accompanying arteriosclerotic changes in the larger branches. The sclerotic changes in the small arteries produce narrowing and even obliteration of the lumen, thereby causing an increase in the pulmonary blood pressure, followed by dilation and hypertrophy of the right side of the heart and finally cardiac failure. There are no antecedent pulmonary or cardiac changes, and, according to Steinberg,[1] the use of the term primary sclerosis of the pulmonary artery is justified only when arteriosclerosis of the greater circulation is minimal or entirely absent.

Secondary sclerosis of the pulmonary artery is considered to result from mitral disease, cardiac abnormalities, emphysema, pleural adhesions, chronic bronchitis, or it may be incidental to a generalized arteriosclerosis.

In the periodical literature certain cases of sclerosis of the pulmonary artery are referred to as Ayerza's disease. It is probable that some of these are primary and some secondary. The syndrome, Ayerza's disease, characterized by dyspnea, cyanosis, polycythemia and hypertrophy of the right heart, was described by Ayerza in 1901 in his lectures at Buenos Aires. He recognized the pathology of these cases as arteriosclerosis of the pulmonary artery, and spoke of the patients as "black cardiacs". Syphilis is considered a prominent etiological factor in this disease, but two opposing views are advanced with regard to the time of onset of the sclerosis, the discussion turning on whether the disease is primarily caused by the arteriosclerosis of the pulmonary artery, or whether the sclerosis is secondary to antecedent changes in the lung. In Ayerza's disease, Escudero[2] maintains that chronic syphilitic bronchitis is the first phase, characterized by polycythemia, and that the second phase presents, in addition, sclerosis of the pulmonary artery, peribronchial sclerosis and hypertrophy of the right heart. This view receives the support of Brachetto-Brain[3] who thinks that the term, Ayerza's disease, should be restricted to cases in which each of the two phases is complete, the chronic broncho-pneumopathy with pro-

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†Received for publication, August 10, 1931.

nounced polycythemia and the chronic cardio-angiopathy with insufficiency of the right heart. In a review of cases of Ayerza's disease, Cheney[4] also states that a definite preliminary stage is apparently necessary for the final development. This essential antecedent is a chronic bronchitis of from one to twenty-five years duration; and Staffieri[5] defines Ayerza's disease as a condition that occurs in young people or persons of mature age whose history reveals a bronchial affection, extending over a long period of time, accompanied by bronchopulmonary sclerosis and emphysema and a sclerosis of the pulmonary artery. The possibility of advanced secondary sclerosis should be borne in mind in considering cases of Ayerza's syndrome, because secondary sclerosis, while usually confined to the larger branches of the pulmonary artery, may in advanced cases affect the smaller arteries and give rise to the same symptoms that are produced by primary sclerosis.

Arrillaga,[6] however, concludes that in Ayerza's disease, sclerosis of the pulmonary artery is primary and due to the *Spirochaeta pallida*, and that the arterial changes may or may not be accompanied by lesions in the bronchi and lungs, and that when lesions occur in the bronchi and lungs they are secondary to the sclerosis of the pulmonary arteries. Since Ayerza's disease is a term that has probably been used to designate both primary and severe secondary sclerosis of the pulmonary artery, it is probably better to distinguish cases as primary or secondary.

In the pulmonary artery arteriosclerotic changes of a moderate degree are not uncommonly seen at the necropsy table, incidental to a generalized arteriosclerosis or as a result of chronic cardiac and pulmonary lesions, and according to Warthin[7] such secondary changes are without clinical significance. Cheney,[4] Miller,[8] and Rosenthal[9] distinguish primary and secondary arteriosclerotic changes in the pulmonary artery; in the primary type the smaller arteries are affected and in the secondary type the medium-sized and larger vessels are involved. Hare and Ross,[10] in a review of the literature on sclerosis of the pulmonary artery, admit the occurrence of sclerosis as a complication of some antecedent cardiac or pulmonary condition, but they have collected twenty-three fully reported and authentic cases of a group in which the signs and symptoms were due to alterations in the pulmonary arteries themselves and in which no antecedent cardiac, pulmonary or bronchial lesions were present. To this group they add one of their own. They emphasize in the primary type the occurrence of obliterative endarteritis of the small arteries which may be followed by dilation and atheroma of the larger vessels. Rosenthal[9] considers primary arteriosclerosis of the pulmonary artery a definite clinical entity and in a study of three cases, he found the most pronounced changes in the small arteries with evidence of progressive changes to the medium-sized and larger vessels. Giuffrida[11] distinguishes primary arteriosclerosis with productive changes, with a tendency to obliteration of the lumen of the small arteries, from secondary sclerosis that results from hypertension in the pulmonary circulation. In primary sclerosis changes in the medium-sized and

larger arteries need not necessarily occur.[9,10,12]

From this review it is evident that there is general agreement that sclerosis of the pulmonary artery may be secondary to changes in the heart and lungs, as mitral disease, emphysema, pleural adhesions and chronic bronchitis and also may be incidental to generalized arteriosclerosis. When sclerosis results from these conditions it is the main trunk and larger branches that are affected by the usual arteriosclerotic changes, intimal thickening and degeneration, medial degeneration and dilation of the vessels. These changes are as a rule without clinical significance, or are overshadowed by symptoms that are produced by the primary disease.

There is also recognized, as an entity, primary sclerosis of the pulmonary artery, affecting the small branches and obliterative in type, and this form is frequently accompanied or followed by arteriosclerotic changes in the larger branches. This type of arteriosclerosis has been compared to the arteriosclerosis affecting the small arteries of the kidney.[1] Primary sclerosis of the pulmonary artery is rare and unless borne in mind can easily be overlooked clinically. It is more common in males and occurs in adults usually before the sixth decade. The changes in the arteries are responsible for the signs and symptoms, such as cyanosis, polycythemia, dyspnea, hemoptysis, and frequently somnolence, vertigo and heart pain; anasarca and passive congestion of the liver, spleen, kidneys, and intestines follow; dilation of the right side of the heart and usually dilation of the trunk of the pulmonary artery are evident. Cyanosis may precede the cardiac failure by several years.[9,13] The specific findings at necropsy are arteriosclerosis of the small pulmonary arteries with varying changes in the alveoli and the bronchi of a fibrotic nature, and dilation and hypertrophy of the heart, particularly of the right side.

The etiology is not clear. Syphilis is given the prominent rôle by many authors,[2,6,10,12,14,15] but the possibility of damage due to the inhalation of gases and particulate matter is suggested by Rosenthal,[9] and in a case reported by Staffieri[5] the patient was a heavy smoker. Rheumatism may also be considered an etiologic factor. Von Glahn and Pappenheimer[16] have described changes in the arterioles of the lungs in cases of rheumatism and they state that the healed lesions may develop a picture that simulates obliterative endarteritis. In a case reported by Steinberg[1] the symptoms of sclerosis were preceded by a severe rheumatic polyarteritis. Giuffrida[11] thinks that the arteriosclerosis of the pulmonary circulation is of a constitutional type.

For the purpose of clarity it is convenient to consider sclerosis of the pulmonary artery as showing the same types of sclerosis that are observed in the systemic arteries. Syphilitic mesarteritis has been described,[7,17,18] and the changes in the pulmonary artery are identical with those seen in the aorta, affecting as they do the first part of the pulmonary artery. Ordinary atherosclerosis occurs in the pulmonary artery and involves the larger branches; it is usually secondary to cardiac or pulmonary changes or incidental to a generalized arteriosclerosis. And finally an obliterative endarteritis of the smaller arteries occurs, which may or may not be associated

with lesions in the larger vessels. This type is of importance because of the resistance offered to the pulmonary circulation. Cardiac failure follows.

Case Report

The patient, a negro male, 40 years of age, was first admitted to the University Hospital, October 11, 1926. He was a tinner by trade and was not accustomed to hard manual labor. There was a history of gonorrhea but not of syphilis. There was no history of respiratory infections prior to the onset of the present illness. His first symptoms were those due to congestive heart failure, and set in four months prior to his admission to the hospital. The chief complaints were shortness of breath, cough, hemoptysis, dizziness and swelling of the legs. At the time of admission the clinical picture was that of a severe cardiac break, with failure of the right side of the heart and the usual signs and symptoms of visceral passive congestion. After the establishment of compensation he was discharged November 6, 1926. There were thirteen subsequent admissions with only slight variations in the clinical picture. On one admission the red cell count was 6,000,000; on three admissions, 5,000,000 or above; on four, 4,500,000 or above; and on six admissions, between 4,000,000 and 4,500,000. While the red cell count did not invariably present a true polycythemia, in our experience with negro cardiac patients, a red cell count of 4,000,000 is above the average. The blood pressure varied between 170/135 and 110/85, a constant low pulse pressure and high diastolic pressure. On three admissions cyanosis was recorded as an objective sign. This is of particular significance because the patient was a negro and cyanosis can easily be overlooked in one of this race. Right sided heart failure was dominant in all fourteen admissions. The blood Wassermann reaction varied: on two admissions it was ++++; once, +++; once, +; and negative at other times. On the eleventh admission the Kahn reaction was ++. In the early course of his illness, over a period of eleven months, he received three injections of neoarsphenamine of 0.6 gm. each, without evident improvement. The cardiac breaks occurred at shorter intervals during the course of observation, and the establishment of compensation became increasingly difficult, necessitating massive venesections

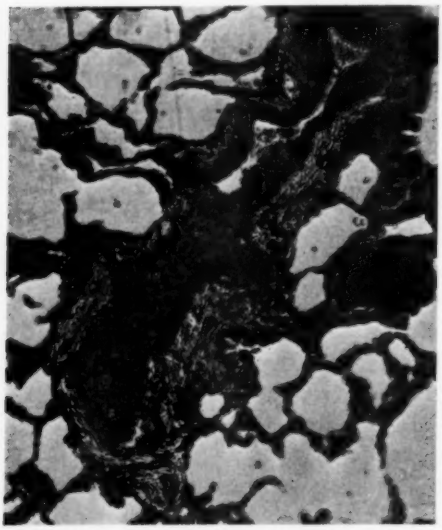

Fig. 1. Longitudinal and cross section of a small pulmonary artery; the media is hypertrophied. There is a nodular thickening of the intima, almost occluding the lumen. x 250.

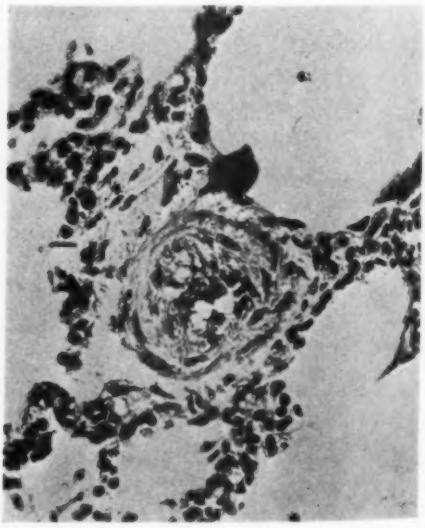

Fig. 2. Cross section of a pulmonary arteriole. The intima is thickened and the lumen is almost obliterated. There are small areas of degeneration of the intima. x 500.

during the last three admissions. The patient succumbed March 11, 1931, approximately five years after the onset of symptoms. A necropsy was performed three hours after death.

Necropsy. The body was that of a well nourished negro male of some 45 years of age, 172 cm. in length, and of estimated weight of 95 kg. There was considerable edema so that the skin was tense. The superficial veins of the neck were distended. A slight excess of clear fluid was found in the peritoneal, and both pleural, cavities. A few fibrous adhesions bound the bases of the lungs to the parietal pleura. The lungs were heavy and soggy, and crepitant throughout. The cut surfaces were dark red, much fluid blood flowed from the cut vessels. There was 100 c.c. of clear fluid in the pericardial sac. The heart weighed 675 gms. All chambers were dilated and filled with blood, on the left side fluid, and on the right coagulated. The endocardium was smooth but in the left atrium and ventricle it was slightly thickened. Of the valves there was nothing noteworthy. The measurements in centimeters of the valve orifices were as follows: aortic, 7; pulmonary, 7.5; mitral, 12.5; and tricuspid, 15 cm. The wall of the left ventricle was 1.7 cm. in thickness and of the right ventricle, 0.5 cm. A few yellow patches were seen in the intima of the aorta, increasing in number downward. The wall of the inferior vena cava was noticeably thickened. A few raised yellow patches were seen in the intima of the coronary arteries. There was passive congestion of the liver, spleen, kidneys, and intestines.

Microscopical sections revealed nothing noteworthy except in the lungs. The most striking change in the sections from the lungs was the prominence of the small arterioles. They were tortuous and the walls were thickened, the thickening being due to an increase in the width of the media. Both the muscle and the elastic tissue of the media were hypertrophied. The lumina were narrowed. In some of the smaller arteries and in the arterioles there was an increase in the thickness of the intima due to fibrosis. Occasionally the lumen of a small arteriole was almost obliterated by a proliferation of cellular connective tissue, in which were small endothelial lined spaces. Rarely thrombi were observed. The adventitia of the arteries and the veins was increased. A few small veins contained thrombi. There was an increase of the connective tissue of the walls

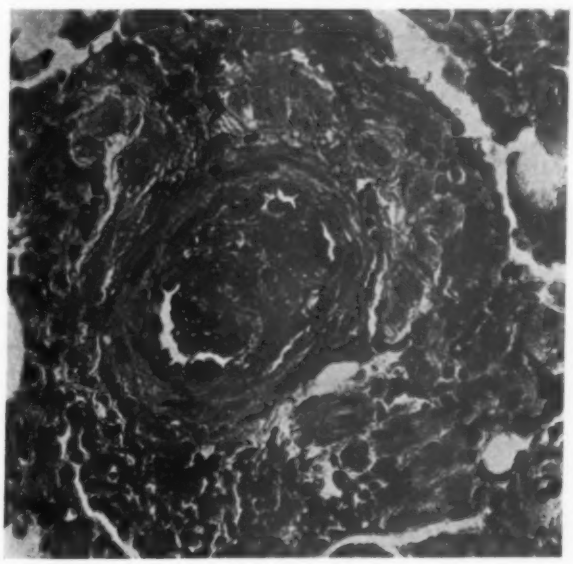

FIG. 3. Cross section of a pulmonary arteriole. The lumen is obliterated by connective tissue which contains vascular spaces. x 500.

of most of the alveoli and sometimes the capillaries were obscured, the wall appearing as an avascular thin layer of hyaline connective tissue. The connective tissue about the bronchioles was increased, the lumina of the bronchioles narrowed, and the folds of the mucosa exaggerated. The muscularis of the bronchioles was hypertrophied. After prolonged search no *Spirochaeta pallida* were found in sections from the lungs.

Comment

From the history, clinical course and the pathology of this case the term primary sclerosis of the pulmonary artery is justifiably used. Such changes as were seen in the bronchi, lungs and heart were secondary to the sclerosis of the arteries. On some occasions the Wassermann reaction was positive but no specific lesions were found at necropsy and, although the necropsy was performed soon after death, *Spirochaeta pallida* were not found in the lungs or in the lesions of the arteries of the lungs. There was no significant etiologic factor brought to light in the history.

Congenital hypertrophy of the media or faulty development may predispose the small pulmonary arteries to the obliterative changes that are observed in these cases.

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Gonococcal Endocarditis*†

Summary of the Literature and Report of a Case

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Thayer,[1] in 1922, stated that "gonorrheal cardiac infections as a whole are by no means very unusual". In contrast to the wide prevalence of gonorrheal urethritis this cardiac complication is rare. Thayer, at that time, reviewed the literature and reported seventy-two cases including twelve new ones of his own. In a comprehensive survey of the literature since 1922 we can find reported only eight authentic cases, to which we add another.

Case Report

A white woman, aged 19, maid, was admitted to the Santa Fe Coast Lines Hospital, Los Angeles, on July 13, 1930, as convalescent from an operation for acute appendicitis. The operation had been performed at Phoenix, Arizona, on July 2, 1930. She had been seized with abdominal pain, nausea, and diarrhea on July 1, 1930. Her temperature previous to operation was 101.4° F., pulse 116, respirations 22. Leucocytes were 17,950, with polymorphonuclears 89 per cent. Rigidity and pain were localized to the right lower quadrant. Laparotomy was performed the next morning, and an enlarged, moderately distended, hyperemic appendix was removed. The pelvis was examined at the request of the patient, and a retroverted uterus, but no other pathology, found. The post-operative course was stormy, with fever to 105.4° F. A blood culture was taken at this time and was reported sterile. On July 12th, ten days after operation, she was transported from Phoenix to Los Angeles.

Physical examination, on admission to the hospital, revealed a small, fairly well developed young female, 5 feet 4 inches tall, weighing 110 pounds. Scalp, no abnormalities. Eyes: pupils reacted to light and distance. No jaundice, strabismus or nystagmus. No exophthalmos or lid-lag. Conjunctivae were of fair color and free from petechiae. Fundi revealed no abnormalities. Nose and Ears: showed no abnormalities. Mouth: tongue dry and coated. Tonsils hypertrophied. Mucous membranes injected. Herpes simplex limited to the left side. Neck: bilaterally enlarged cervical glands. No venous fillings or pulsations. Thyroid not enlarged. Lungs: equal movement; normal resonance. Breath sounds vesicular. No râles. Heart: no demonstrable hypertrophy to percussion. Rate 106, regular, P_2 greater than A_2. Blood pressure 110/70. Abdomen: draining operative wound in right lower quadrant. Liver and spleen not palpable. No masses. Extremities: no clubbing, tremors or deformities. There was marked hyperextension of the elbows. Reflexes: knee jerks, ankle jerks, biceps, triceps and abdominals, present, equal, and active. Skin: normal texture, somewhat pale. Pelvic examination not done. Urine: cloudy; specific gravity 1024; acid; sugar absent; albumin trace; acetone absent; moderate number of pus cells; a few epithelial cells; no casts. Blood: hemoglobin 67 (Sahli); red blood cells 4,200,000; white cells 13,200, with 81

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†Received for publication, August 10, 1931.

per cent polymorphonuclear neutrophiles, 8 per cent lymphocytes, 11 per cent large mononuclears. Wassermann test negative.

The temperature of 100° F. on admission ranged from 98.4° to 100° F. during the first ten days. Drainage from the abdominal wound persisted. At times, a scanty vaginal discharge was noted, and a cervical smear contained a moderate number of gram-negative intracellular diplococci, morphologically gonococci. The patient developed bilateral lower abdominal pain and it was thought that a salpingitis might be present. Hot vaginal douches gave relief.

July 23: hemoglobin had dropped to 58 (Sahli), red count 4,020,000, white count 9,200, with 81 per cent polymorphonuclear neutrophiles. Temperature is recorded in chart reproduced as figure 1.

A blood culture taken July 30, and planted on Swartz agar plus one-third hydrocele fluid, remained sterile. Smear for malaria was negative. Quinine sulphate had no effect on the fever.

By August 3 the abdominal wound had stopped draining and was closing.

August 5: hemoglobin was 48 (Sahli); red blood count, 3,510,000; white blood count, 9,800 with 75.5 per cent polymorphonuclear neutrophiles. The red cells showed a slight degree of achromia.

August 8: 400 c.c. of whole blood was given.

August 10: the genito-urinary consultant stated, "Purulent discharge from urethra. Moderate cervical discharge. Bartholin glands not involved. Neither tube palpable. No evidence of abscess. Complains of some frequency and burning. This is due to the urethritis. Advise no local treatment until she is able to be up."

August 15: hemoglobin was 51 (Sahli); red blood count, 3,610,000; and the white blood count, 14,300, with 82 per cent polymorphonuclear neutrophiles.

August 26: patient was seen by one of us and the following note made: "After period of fever for thirty-two days post-operative with leucocytosis, negative blood culture, no definite petechiae, clubbing, heart murmur or palpable spleen, temperature subsided for three or four days, then recurred. There is a progressive secondary anemia. The spleen is now definitely palpable. A loud blowing systolic murmur can be heard at the apex: whether due to anemia or endo-

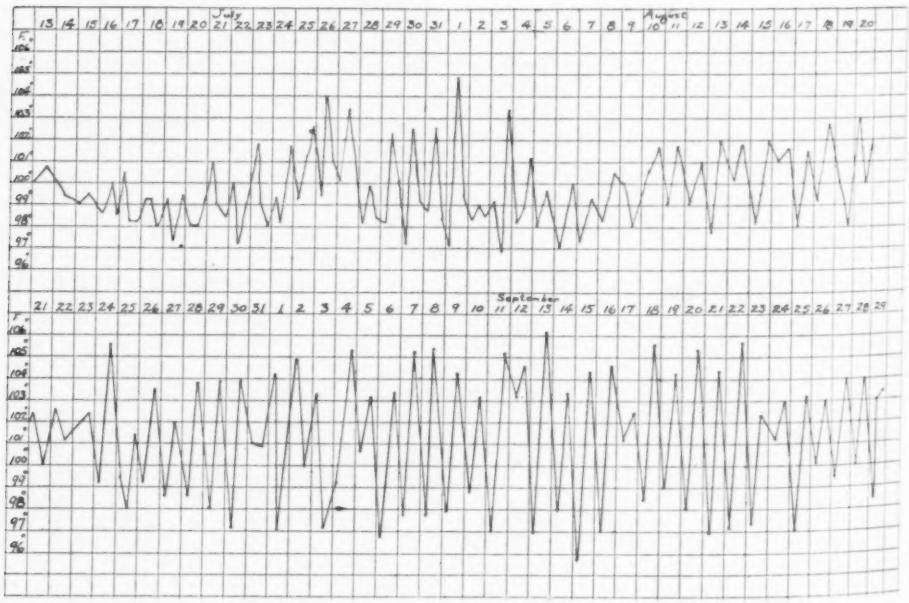

FIG. 1

carditis cannot be stated. There are no visible petechiae but there is suggestive clubbing of fingers. Blood culture to be repeated for gonococci." Hemoglobin, on this date, 38 (Sahli); red blood count, 3,000,000; white blood count, 7,400, with 87.5 per cent polymorphonuclear neutrophiles.

September 3: three petechial spots found on the left hand.

September 5: hemoglobin, 33 (Sahli); blood count, 2,480,000; white blood count, 5,100, with 83 per cent polymorphonuclear neutrophiles.

September 6: transfusion of 350 c.c. whole blood.

September 9: laboratory reported as follows: "Blood cultures on Swartz agar plates with hydrocele fluid were sterile after seven days. Glucose broth with an equal amount of hydrocele fluid incubated four days and transplanted to Swartz hydrocele slant showed positive culture in 24 hours. Organisms were gram-negative, biscuit-shaped diplococci in pure culture. Culture positive for gonococci."

September 9: progress note by one of us: "Blood culture for gonococci finally positive on second culture. Change in heart murmur. Definite diastolic blow localized to third and fourth interspaces to left of sternum." Electrocardiogram showed sinus tachycardia. Rate 100, with upright P, T and QRS complexes in all leads. Patient was too ill to do an orthodiagram.

September 12: hemoglobin, 29 (Sahli); red blood count, 1,980,000.

September 13: transfusion 500 c.c. whole blood.

September 15: hemoglobin, 32 (Sahli); red blood cell count 2,060,000.

September 17: acriflavin hydrocloride, 0.3 gm., given intravenously. A transfusion of 500 c.c. of whole blood from a patient convalescent from gonorrheal arthritis was administered. On this date, a third blood culture was taken and was reported positive for gonococci, thus making the second positive culture.

September 19: hemoglobin, 38 (Sahli); 2,180,000; white blood count, 6,400, 83 per cent polymorphonuclear neutrophiles.

September 21: acriflavin hydrochloride, 0.45 gm. intravenously.

September 24: "Sudden hemoptysis today. Probable pulmonary infarct. Several new petechiae on anterior chest wall. One in right lower lid has disappeared."

September 26: "Condition grave. Innumerable petechiae. Marked clubbing of fingers present."

September 29: patient died.

Autopsy performed by Coroner's Surgeon John H. Schafer, September 30, 1930, was reported as follows:

"I performed an autopsy on September 30, 1930, at the Los Angeles County Coroner's Mortuary, and found the body jaundiced, graded three. There were many petechiae in the skin over almost the entire body.

"Upon opening the body, the heart was found to be about normal in size and there was a purulent pericarditis. Smears from the pericardial exudate revealed no organisms. The epicardium showed numerous petechiae and there were a few petechiae in the myocardium. The leaflets of the mitral valve were the site of large vegetations (see figure 2) and smears from these revealed large numbers of gram-negative, intracellular diplococci morphologically identical with the gonococcus. No other gross lesions of the heart were found.

"Both lungs showed an extreme degree of congestion and edema with innumerable small hemorrhagic foci, with many small pin-point abscesses in the center of the hemorrhagic foci. The hilus of the right lung showed what appeared to be a beginning infection by direct extension from the adjacent pericardium.

"The spleen weighed 800 grams, was very soft and showed many large infarcts.

"The kidneys were about normal in size and the right one showed a number of small septic infarcts.

"The liver was jaundiced, pale, and there was a fibrinopurulent deposit on the right dome.

"The intestines in the lower portion of the abdomen were covered with a light fibrinopurulent exudate and were lightly adherent. The appendix was missing. The uterus and adnexa were covered with a similar exudate and were lightly adherent to the surrounding structures. The tubes and ovaries showed no gross lesions except the exudate described. The uterus was very small, sharply anteflexed, and the cervical canal

showed the typical palmate folds of the virgin uterus. The uterus had not been pregnant. There is a history of recent positive smears for gonococci from the cervix."

Since Thayer's review of the subject of gonorrheal endocarditis in 1922, there have been in all nineteen case reports of so-called endocarditis with gonococci as the etiological agent. We say "so-called" because of the lack of absolute evidence culturally in most of these case reports. Thayer admits the necessity of positive blood culture intra-vitam, or post-mortem culture from the heart valve, for diagnosis. In the twenty cases which he reports from the Johns Hopkins Hospital records, fourteen were so proved. Six had negative blood cultures intra-vitam and only bacterioscopic evidence of gonococci on the heart valves post-mortem. All of these cases, however, had either a specific urethritis or positive smears from the cervix uteri. They, therefore, are presumptive cases, only; probably satisfactory clinically but not bacteriologically.

We hold with Karsner[2] that "gonococcal endocarditis must show the presence of gonococci in the blood or lesion to be accepted as such." We would further add that the determination of gonococci from the lesion, post-mortem, is certain only by culture. Either positive intra-vitam culture or post-mortem culture from the lesion is essential to an absolute etiological diagnosis. Smears from the heart lesions without culture and with

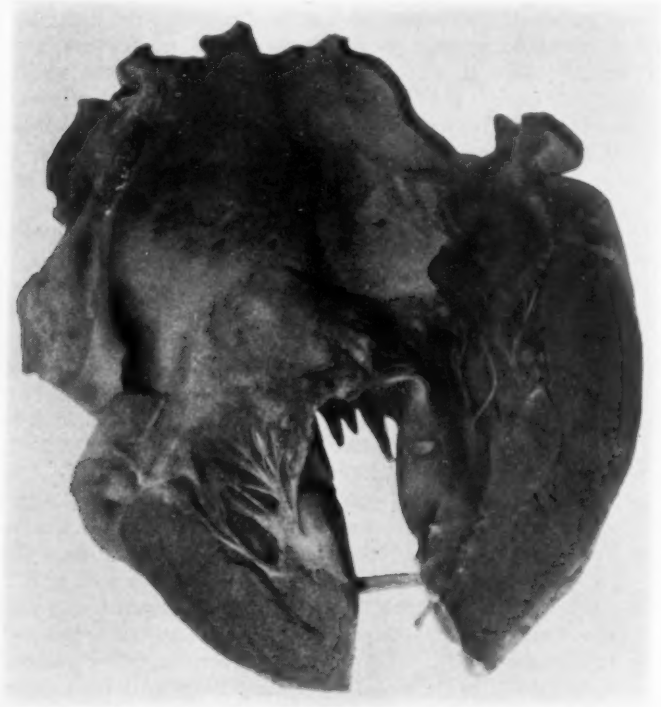

FIG. 2

negative blood culture intra-vitam would be presumptive evidence only.

In dealing with gram-negative diplococci, the difficulty of differentiation between gonococci and meningococci must be considered. Only within recent years have the cultural differences between these two organisms been made with any degree of certainty. This differentiation is particularly important in view of the numerous recent case reports of meningococcus septicemia with or without endocarditis; most of the cases without meningitis. On clinical grounds there seems little possibility of confusing these two types of septicemia. As stated above, Thayer's negative blood and valve culture cases all had specific urethritis or cervicitis as a point of differential diagnostic value clinically. The not infrequent association, however, of positive gonococcic urethritis or cervicitis and an endocarditis due to a secondary invading organism, as the streptococcus, staphylococcus, or pneumococcus, must be kept in mind. It is in cases of this type, with negative intra-vitam blood cultures, that the possibility of error in considering them instances of gonorrheal endocarditis arises.

Cases reported by Aubertin and Gambillard;[3] Villela and Torres;[4] Bard, Langernon and Gardère;[5] Gallois;[6] Edwards;[7] Johnston and Johnston;[8] Kramer and Smith;[9] McCants;[10] Klein;[11] Lion and Levy-Bruhl;[12] and Herzog and Kouzmin,[13] all lack positive blood cultures intra-vitam or positive cultures from the post-mortem lesions. Most of them can be classed as clinically presumptive but unproved cases.

Authentic culturally proved cases have been reported since 1922 by Gallois,[6] Barbe and Meynet,[14] Riecker,[15] Brebner,[16] Pratsicas,[17], Vander Veer,[18] Kramer and Smith,[9] and Perry.[19] These eight with our one case make only nine authentic cases since Thayer summarized the literature in 1922. The seventy-two cases which he reviewed included at least six which were presumptive only; making a total to date of only seventy-five culturally proved cases. This small number is in striking contrast to the wide prevalence of gonococcus infection. Of Thayer's reported group only five cases recovered. Since his report only one instance of recovery can be found. Repeated small transfusions seemed to be the factor of importance in the recovery in this instance. In our patient, similar transfusions were of no avail. Tabbutt[20] reported two instances of gonococcus septicemia with positive intra-vitam blood cultures without endocarditis, both proved at autopsy. Such findings emphasize the importance of autopsy confirmation of the presence or absence of endocarditis in the presence of culturally proved septicemia.

The value of complement fixation as a diagnostic aid in gonococcus endocarditis is questionable. Because it raises this question and also because of the relative inaccessibility of the article, we summarize the case report of Herzog and Kouzmin,[13] of Moscow.

An adult male developed an acute urethritis on November 1, 1926. Under local treatment the discharge subsided but the patient persisted in running a temperature from 37° to 40° C. for almost three months. On December 29 a blood culture was sterile. A systolic murmur developed. He suffer-

ed pain in the left kidney region, interpreted as due to an embolus. Complement fixation reaction was positive. Autopsy on February 9, 1927, demonstrated a vegetation on the mitral valve. Smears or cultures are not reported. They base their diagnosis of a gonococcic endocarditis on the presence of the urethritis, continued fever, systolic murmur, vegetation on the mitral valve, and a positive complement fixation test. In what manner the complement fixation reaction can be considered specific for gonorrheal endocarditis we do not know. It seems reasonable to presume that gonococcic urethritis alone would make it positive, and so include this case report, as one of the presumptive clinically but unproved culturally cases of gonococcal endocarditis.

Summary

1. The literature on gonococcus endocarditis is summarized to date. The eight authentic cases reported since 1922 are reviewed. To these we add another. They make a total of seventy-five proved cases of gonococcus endocarditis in the literature.

2. The criteria of diagnosis are discussed. A positive diagnosis of gonococcal endocarditis can be made in the presence of clinical evidence of endocarditis only when intra-vitam blood cultures are positive for gonococcic or when cultures from postmortem lesions reveal the same organism.

Since the writing of this article an additional authentic case of gonoccal endocarditis, proved by postmortem culture, has been reported by H. B. Kirkland.[21]

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The Value of Knowledge of Personality

"FORECASTING the future of body-minded man, and not a decapitated being, is an interesting and, on certain occasions, a wise precautionary measure. We should not, however, allow our forecasting proclivities to divert attention, as so frequently happens today, from the importance of acquainting ourselves with the knowledge that can be readily obtained from reviewing the data supplied by heredity, environment, physical characteristics, the nature of the emotional and mental reactions, the habits of life, the tendencies to face or dodge reality, academic tests, estimates of intelligence, and information bearing on the social environment and the reactions of the individual to the people with whom he is brought into contact. Without this information we can only try in a very bungling manner to direct the expenditure of human energy. Unless we have definite information in regard to the individual personality, we can only expect to make ridiculous attempts to fit young people for school, college, business, industry or life. Without this information we should not expect to be much more successful than we are at present in fitting children into home surroundings, struggling students into academic environments, apprentices into their trades, business men into bigger business enterprises, and misfits of various kinds into ociety.

(From *Prohibiting Minds and the Present Social and Economic Crisis*, by Stewart Paton, M.D., Paul B. Hoeber, Inc., New York City.)

The Significance of Lymphatic Tissue and Adenoma-Like Areas in the Thyroid Gland* ** †

By L. R. Himmelberger, Ph.D., *Flint, Michigan*

While the terms Graves' disease, Basedow's disease and exophthalmic goiter are purely clinical expressions and their use in pathological connections perhaps questionable, no suitable pathological term exists that is descriptive of the changes seen in the thyroid gland in this disease. Parenchymatous hypertrophy and hyperplasia have been used quite properly but these expressions do not describe the most important changes seen, as we hope to show. The present clinical tendency to consider "toxic adenoma" as a condition separate from Graves' or Basedow's disease also lends confusion to a pathological understanding of the process in the thyroid gland.

The association of thyroid disease with a general lymphadenopathy and the idea that in some way or other it was related to changes in the thymus is by no means a recent conception, for as early as 1905 Hansemann[1] reported four cases of Basedow's disease coming to necropsy in which a general lymphatic hyperplasia was observed. At that time he suggested a relationship between thyroid and "status lymphaticus." In 1908 Capelle[2] also took a similar attitude and in 1911, with Bayer,[3] reported beneficial results from thymectomies on Basedow patients. Bircher,[4] in 1912, reported experiments in which he produced Basedowian symptoms in dogs by implantations of thymus glands from patients suffering from thyroid disease. Pettavel[5] wrote on the pathological anatomy of Basedow's disease in four well studied cases. In two cases he found a persistent thymus; in all he found areas of lymphoid tissue in the thyroid gland, and in three there existed a general hyperplasia of the lymphatic tissue throughout the body. He failed, however, to place diagnostic significance on the lymphoid hyperplasia in the thyroid. Matti[6] reported necropsies on ten cases in which general lymphoid hyperplasia was a striking feature. In but one case did he fail to find lymphoid follicles in the thyroid. This patient was a twelve year old child however, and one may properly question the existence of Graves' disease. Rautmann,[7] also studying the pathological anatomy, demonstrated a general lymphadenopathy with lymphocytic infiltration in the thyroid. Pettavel[8] reported addi-

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**Thesis presented to the Faculty of Michigan State College, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

†Received for publication, April 15, 1931.

tional work in 1914; and Klose,[9] in 1916, also called attention to the general lymphoid hyperplasia existing in thyroid disease.

In this country many writers have mentioned the presence of pseudo-nodes, lymphatic tissue, round cell infiltration, etc, in the thyroid gland. McCallum's[10] is the only text book on General Pathology which refers to these areas. He says that definite lymphoid nodules are found in exophthalmic goiter and but rarely if ever found in normal glands. He fails however to ascribe any significance to their presence. Aschoff,[11] while lecturing in this country, spoke of the presence of pseudo-nodes in both Basedowian and non-Basedowian glands, and observed that they are more frequently found in glands from Basedow patients. Sager[12] mentioned the presence of lymphocytes, but evidently did not consider them of significance. Rienhoff[13] gave them a place in the pathological picture of thyroid disease, but evidently did not consider them to be of diagnostic importance. Broders[14] has always considered them to be evidence of thyroiditis. Menne, Joyce and Von Hungen[15] also believed them to be of inflammatory origin. Warthin[16] was the first in this country to point out the pathological significance of areas of lymphatic hyperplasia. He alone at that time (1924) considered rudimentary lymphoid areas as being of diagnostic importance, thus definitely suggesting a new diagnostic criterion in Graves' disease, the essential pathological changes of which have been considered, for nearly 40 years, to rest exclusively in the acinar epithelium and amount of contained colloid. It was Warthin's observations that first engaged the writer's interest and stimulated the study in this laboratory. Elovzin[17] working here in 1927 made a limited study of our material then available. It was Warthin's contention in 1924 and again in 1929 that the presence of lymph tissue was diagnostic of potential Graves' disease or exophthalmic goiter. He gave further impetus to the idea held by the previously quoted continental observers that this tissue indicates a definite pathological constitution, the so-called thymico-lymphatic type of individual, or as he preferred to call it, the "Graves' constitution". He pointed out that these individuals present a hyperplasia of the lymphoid tissue throughout the body and took the position that they have a congenital predisposition to Graves' disease. In a recent survey of one hundred and eighty-one post-operative cases, Clarke and Black[18] also concluded that a constitutional factor is involved. Simpson[19] supports this view in a study of 665 resected thyroids. On the other hand, Hellwig[20] in a recent article opposed Warthin's views, basing his conclusions on a study of fifty-eight surgical and seven postmortem specimens. He concluded that the presence of lymphocytes in the thyroid is the result of a simple local reaction to hyperactivity of the gland, that they are of no diagnostic importance and can in no way be interpreted as evidence of a so-called Graves' constitution. Sixty-six per cent of his cases presented lymphocytic infiltration and he cites a group of cases without clinical symptoms in which these areas were present in

38.5 per cent. He does not state the reasons or indications for the surgery in this latter group. One is led to believe that he assumes lymphocytic infiltration to be present in 38.5 per cent of normal glands.

It is the purpose of this paper to present an interpretation of the significance of lymphatic tissue in the thyroid gland as gained from a study of material collected over a period of six years, consisting of (1) thyroids from stillborn infants, premature births, and very young children coming to necropsy, (2) surgically resected thyroid glands and, (3) necropsy material from older subjects who died from conditions not in anyway involving the thyroid gland, together with observations on the so-called adenomata of the thyroid.

If Warthin's thesis is tenable, that there exists a definite type of individual possessing a "Graves' constitution," who is potentially a case of exophthalmic goiter, that constitution must be congenital and the significant lymphatic areas should be present at birth or even in uterine life. A routine search of thyroids of young subjects should, therefore, be rewarded with a certain percentage incidence of the lesion. Material for this section of the study consists of thyroids from 140 full term, premature and still-born infants. Further, if the lesion under consideration is a part of the "Graves' constitution", and is of diagnostic significance, it should be present in all cases of true Graves' disease and it should be capable of demonstration in practically all resected glands from such cases. This material consists of three hundred and eighty-six glands removed surgically. Still another point of proof susceptible to demonstration rests in a study of supposedly normal glands obtained at necropsy.

According to Warthin's thesis not all of those individuals possessing this "Graves' constitution" develop clinical Graves' disease. It should, therefore, be possible to show a small incidence of the lesion in question in postmortem material from subjects devoid of thyroid history. While this incidence should be less, it should be roughly comparable with that found to be existent in the glands of infants, prematures, etc. Our material studied in this connection consists of glands from two hundred cases selected from the standpoint of a nonthyroid history.

The normal thyroid has been quite intensively studied by many workers. No attempt will be made here to present a review of this literature. Suffice it to say, that in all the literature consulted, no mention is made of the presence of lymphatic tissue in the normal thyroid except by Marine,[21] who said merely that lymphocytes do occur normally. He dismissed the subject with a single sentence and failed to state the extent to which it was observed.

Williamson and Pearce[22] in an extensive study of the normal gland made no mention of lymphoid tissue. Rienhof,[23] working with serial sections and using reconstruction methods, said nothing of their presence in normal glands. In view of the fact that lymphoid areas failed to attract the attention of most investigators of the normal gland, one may feel safe in assuming that such tissue is not a com-

mon histological component of the normal thyroid.

Study of Infant Thyroids

This material, as before stated, was secured from premature fetuses, still-born infants, and infants that lived but a short time after birth. Most of the material came from still-born infants, but we have several specimens from fetuses as young as the fifth month of gestation. In passing, it is perhaps of interest to note that colloid was present in the acini of these fetal thyroids to a greater or less degree. This is in keeping with the observation of Murray[24] and others quoted by him. A search of the literature reveals few studies of fetal or infant glands; Murray makes no mention of lymphocytes, neither does he speak of adenomata. Rautmann, however, did observe small areas of lymphocytes in rare instances while studying glands from very young children. Warthin also mentioned their occurrence in rare instances. Our study of glands from these cases was confined to a search of microscopic preparations for areas of lymphocytes and to observations on the presence of adenomatous areas.

The histological picture of the thyroid gland from the young subject is quite constant. Maturity of the epithelial cells lining the acini is apparently established prior to birth and colloid storage is a pre-natal function of the gland, at least as early as the fifth month. Murray has shown that post-mortem desquamation of acinar epithelium is responsible for the appearance of acini filled with epithelial cells. This is also our experience. Study of microscopical sections from one hundred and forty glands from the sources above outlined revealed the presence of lymphoid areas in four cases only. Two of these were still-born infants, one was a baby three weeks old, dying from hemorrhagic disease of the new-born, while the other was an infant that lived for but a few hours after birth, death being due to cerebral hemorrhage. These results give a percentage incidence of the lesion of approximately 2.8 per cent. Had more material been available a more accurate incidence would of course have been established, as it is very obvious that in a matter involving low percentages a large mass of material is quite essential. These results, however are indicative of findings that could confidently be expected in a large number of cases. A further consideration of this percentage incidence will be taken up in connection with postmortem material from older subjects. There was one case in which the lymphoid bodies were found which was not included in the series because of the other pathology present. This was a case of a child nine months old, dying a so-called thymic death. This case was previously reported by the writer[25] and the observation made at that time was that no areas of rudimentary lymphoid tissue were found in the thyroid parenchyma. During the progress of this work a re-study of this case was made, new sections were cut and an intensive search revealed the presence of lymphoid areas. This experience points out the necessity of numerous blocks and careful search.

Of the one hundred and forty specimens examined, areas of so-called "fetal" adenoma were observed in three cases. These areas are separ-

ated from the adjacent parenchyma by a thin fibrous connective tissue capsule and there is a definite difference in the appearance of the cellular structure. Little or no colloid is seen in these areas; the cells are very compact, and take a much deeper nuclear stain.

Resected Thyroid Glands

In a study of surgical material, the conclusions at which one may arrive are made difficult by the perplexing question of the clinical diagnosis as recorded on the patient's chart and because of the paucity of the clinical information, for it is upon these clinical records that the comparative study must be based. With the aid of experienced clinicians we have attempted to classify our material into two groups (1) those cases showing undoubted clinical evidence of Graves' disease and (2) those cases in which the data in the record did not warrant such a conclusion, or cases which were definitely diagnosed as not of a Graves' character. The criteria used for the first group were: Tachycardia, exophthalmos, tremor, increased pulse pressure, definite loss of weight and increased basal metabolic rate. Cases showing any three of the above clinical symptoms were considered, perhaps liberally, as true Graves' disease. All others were placed in the second group. It is very obvious that errors in classification are certain to occur inasmuch as the information in some instances was meagre and incomplete, not representing, perhaps, a true picture of all the clinical signs present.

Slides from 386 surgical cases were studied with the following histological findings:

Lymphatic tissue with no epithelial hypertrophy	123
Hypertrophy of epithelium with lymphatic tissue	62
Hypertrophy of epithelium with no lymphatic tissue	4
Hypertrophy, lymphatic tissue and adenoma	12
Lymphatic tissue and adenoma	59
Adenoma, iodization and degeneration	7
Colloid gland only	45
Cystic degeneration without hypertrophy or lymphatic tissue	28
Iodism	46
	386

Examination of the tabulated observations, shows the presence of lymphoid tissue in 246 cases, while epithelial hypertrophy existed in but 68 cases. There were four cases showing epithelial hypertrophy without lymphatic areas. These cases were among our earliest material and but few blocks were available in each case. We feel that had sufficient material been available the lesion could have been demonstrated in these cases. The low incidence of epithelial hypertrophy is in striking contrast to the high incidence of lymphoid areas and represents a valuable feature in the study of these glands. Were epithelial hypertrophy the only pathological change considered as indicative of Graves' disease, a marked difference between clinical and pathological findings would exist, since of the 246 cases showing rudimentary lymphoid tissue, all but eleven had been diagnosed, or showed definite clinical signs of, Graves' disease, as did the four cases showing epithelial hypertrophy only. The eleven cases not classified as clin-

ical Graves' disease were cases with a very meagre history in each instance, with the clinical diagnosis given as "toxic goiter", which would perhaps warrant their classification as Graves' disease since, clinically, this term is often used interchangeably with Graves' disease. Of the other 140 cases, nine had been classified according to our standards as clinical Graves' disease. The fact that these failed to show lesions of the disease is, we feel, due to our liberal clinical requirements or to having "missed" the areas because of an insufficient number of blocks having been taken. Two of these cases were classed pathologically as undergoing degeneration, four as iodism, while in three no definite changes could be detected. The data presented emphasizes the importance of recognizing the presence of lymphoid tissue and its interpretation as a pathological feature of Graves' disease, since practically all cases showing the classical clinical signs of the Graves' syndrome present the lesion in question.

Those glands classified as adenomatous all contained encapsulated areas of atypical thyroid tissue in different stages of development, but no case showing adenomata as the only deviation from normal presented true clinical signs of Graves' disease. The clinical adenoma described by clinicians is not, in our opinion, an adenomatous structure at all but merely represents a nodular portion of the thyroid containing perhaps large amounts of hypertrophic tissue. We have observed in a few cases that the areas of lymphoid tissue are more numerous in these nodular structures than in tissue taken at some distance from the nodular portions. We feel that this accounts for the so-called "toxic adenoma" and the prevailing impression that removal of the "adenoma" gives clinically beneficial results. That there is some doubt as to the permanency of these beneficial results is shown by the recent survey of Clarke and Black.[18]

There were twenty-eight cases of large glands showing no evidence of Graves' disease. These all showed, grossly, areas of degeneration of various degrees, some adenomatous, but consisting for the most part of colloid cysts containing old hemorrhage and softened tissue. A few were undergoing calcareous degeneration and an occasional one showed definite necrosis. It is possible that tissue dissolution products in these degenerated glands may supply a toxic amount of the thyroid hormone and thereby cause symptoms that clinically simulate the Graves' syndrome, thus being responsible for many diagnostic errors. This point seems susceptible to experimental study and experiments embracing it are now in progress.

The forty-six cases reported as iodism demand consideration since the question of iodine-Basedow which formerly occupied a large place in the literature is now receiving but scant attention. According to Crotti,[26] individual sensitivity to iodine varies widely. Many patients tolerate large amounts of iodine, while in others, very small amounts are responsible for marked disturbances. Moreover, some of those who have previously shown good tolerance to iodine preparations suddenly develop pronounced symptoms of iodine-Basedow. In this day of iodine salt (particularly in

Michigan) and proprietary reducing nostrums containing iodine, when practically everyone is receiving iodine constantly or at intervals, it seems to us that the question is deserving of more consideration than ever. Warthin contended that over-iodization will produce clinical signs simulating Graves' disease. Jackson[27] also writes of a type of hyperthyroidism being caused by iodine. In one of our cases diagnosed clinically as Graves' disease by the physician, and having a basal rate of + 30, together with a mild tachycardia and slight loss of weight, we failed to find lymphoid areas. Upon investigation it was found that this patient had previously been using proprietary goiter remedies containing iodine, and had been further iodized by his physician. Histologically, the tissue presented all of the involutional changes described as due to iodinization.

Warthin reported in 1924 an analysis of 976 resected glands. Of these, 247 presented areas of lymphatic tissue while 154 showed both lymphatic tissue and epithelial hypertrophy. A large portion of Warthin's material was collected before the extensive use of iodine as a preoperative therapeutic procedure which no doubt accounts for the greater incidence of hypertrophic epithelium as compared to our results in this connection. The remainder of the cases studied by Warthin showed no evidence of Graves' disease and the physical findings did not warrant such a diagnosis.

The absence of epithelial hypertrophy in a large proportion of the specimens is no doubt due to epithelial involution due to iodine therapy. Many observers including Sager, Rienhoff and Warthin have pointed out the involutional effects of iodine in exophthalmic goiter. At the present time practically all cases of Graves' disease coming to surgery are iodized preoperatively, consequently a non-treated surgical specimen is rare indeed. Rienhoff, in particular, studied the effect of iodine on the involution of thyroid epithelium in exophthalmic goiter. His observations were made upon seven well considered cases in which artificial involution was studied at various stages. He describes the changes due to iodine as follows:

"(a) Increased amount and density of colloid.
(b) Increase in size and regularity of acini.
(c) Increase in amount of connective tissue in the septum and scarring throughout the gland.
(d) Decrease in size and height and change in shape of epithelial cells from a high columnar to a cuboidal or endothelial cell.
(e) Decrease in cytoplasmic bodies or constituents.
(f) Decrease in vascularity of gland.
(g) Decrease in vacuolization of colloid and deposits of lymphocytes."

Warthin believed that overiodinization produces a "watery" colloid and that lymphocytic exhaustion of the germ centers of the lymphoid tissue results. In our experience extensive iodinization also causes marked atrophy of the epithelial cells lining the acini, the cytoplasm is decreased and the nucleus contracted and deformed. We have been unable to show a definite difference in the lymphoid areas in overiodized and underiodized specimens because of our inability to surmount the difficulty of obtaining specimens from the same patient before and after iodinization.

Selected Postmortem Thyroids

In a study of the thyroids from 1000 autopsies Warthin found 32 showing areas of lymphoid tissue. Two of these were also carcinomatous. These findings give a 3.2 per cent incidence of lymphoid areas in a routine examination of all cases coming to necropsy. These cases were evidently not selected with reference to the exclusion of thyroid involvement and possibly included some cases which had previously suffered from Graves' disease.

As before stated we studied slides from 200 cases without thyroid involvement, many of them in the younger age groups (early part of first decade.) In this study we made the following observations:

Epithelial hypertrophy	0
Lymphatic tissue	4
Areas of adenomatosis	9

The percentage incidence of lymph tissue was 2 per cent. While this is considerably lower than Warthin's figures it corresponds to the incidence of these areas found in infants glands, since theoretically the incidence should be higher in the case of the latter. It will be seen that the incidence of adenoma-like areas in selected necropsy and infant material is also within comparable limits.

Adenoma

A study of this surgical material has made possible observations regarding adenoma. Many clinicians consider toxic adenoma a disease independent of Graves' disease, but as before stated, the clinical term "adenoma" has no reference to histology and is applied to nodular forms of thyroids which may not be involved in Graves' disease. Reinhoff from his series of seven carefully studied cases of exophthalmic goiter in which involution was established by the administration of iodine, came to the conclusion that a large proportion of those areas considered adenomata are but residual areas of hypertrophy and hyperplasia which have remained refractive to iodine or because of disturbed vascular supply have not been subjected to its influence. Ewing's miliary adenomata were considered by him to be such areas. He offered as a possible explanation for the failure to secure permanent remission from iodine the suggestion that these areas of persistent hypertrophy maintain a state of hyperthyroidism. Warthin considered the adenoma of the thyroid as a congenital anomaly due to altered vascular supply and therefore altered development results. Ewing considered the fetal adenoma as being embryonal. Menne, *et al.*, considered adenoma as a separate division in their system of classification.

Our observations have disclosed the following facts:

1. Small areas of adenoma-like structures are capable of demonstration in certain slides from infant thyroids. These areas present a cell arrangement distinct from the balance of the tissue.

2. Adenomatous areas, both the so-called "fetal" and mature types, are seen in postmortem material from selected non-thyroid cases.

3. These adenomatous structures are quite as frequently found in non-toxic glands as in so-called toxic cases. Figure 1 shows a gross specimen of adenoma and figure 2 shows an area of lymphocytes in the thyroid tissue outside the encapsulated area at "A".

4. A study of 100 glands from

FIG. 1. Gross specimen of thyroid with adenoma, to show area from which figure 2 was made.

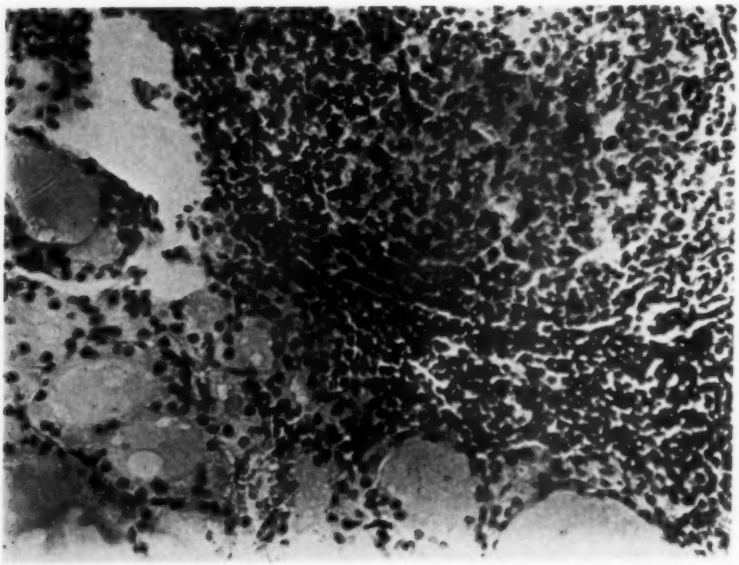

FIG. 2. Photomicrograph showing an area of lymphocytes in the non-adenomatous tissue at 'A' in figure 1.

dogs of all ages and breeds shows the presence of these adenomata in a small percentage of the glands.

In view of the foregoing it appears to us that "fetal adenoma" bears no relation to thyroid disease. We have no cases of adenoma in our material which presented clinical signs of toxicity that were not shown to be Graves' disease, as determined by the presence of lymphoid tissue. The presence of these areas of adenoma-like structure in infant glands would tend to refute the conclusions of Rienhoff that they are persistent hypertrophic areas. Their presence in postmortem material of all ages, as well as in infants lends support to the view of Warthin that they are congenital structures. Their presence in dog thyroids leads to a safe assumption that they are in no way related to Graves' disease, *per se*, as dogs are supposedly not subject to the Graves' syndrome.

Comment

In this study of the occurrence of rudimentary lymphoid tissue and exophthalmic goiter we have included limited observations on the significance of adenomatous areas. The data presented from the examination of infant and selected necropsy material may be taken together when considering Warthin's hypothesis that these pseudonodules are evidence of constitutional deviations from normal. The presence of areas of lymphatic tissue in infant glands is perhaps of greater significance than their presence in the glands from necropsies of older subjects, inasmuch as one is not confronted by the question of pre-existing Graves' disease, although we have tried to obviate this factor in the selection of our necropsy cases. We were unable to follow Warthin's study with reference to a general lymphoid involvement in exophthalmic goiter for the reason that but one necropsy case of exophthalmic goiter was available. In this one case, a female 50 years of age, cervical and mediastinal lymph nodes were enlarged and hyperplastic, the thymus was mildly persistent having a weight of 6 grams and the liver showed marked degenerative change. Menne *et al.* take the position that lymphocytes in the thyroid gland are the result of inflammatory absorption reactions following sustained hyperactivity of the gland and that the "prolonged activity probably leads to the necessity for more supportive stroma". While there might be some defense for this reasoning regarding the presence of this lesion in adult thyroids, it is hardly conceivable that this explanation would hold in cases of infant glands. Furthermore, a considerable number of our specimens came from children succumbing to so-called "summer diarrhea" and it is interesting to note that none of these showed the presence of these areas. It would be a conceivable possibility that were they the result of a true inflammatory process, one would be able to demonstrate their presence in an infectious disease of this type in which there is a marked disturbance of all metabolism, and in which a general lymphadenosis exists. Numerous other childhood diseases were represented in our material and in no case were these areas of lymphoid tissue noted. In a case of miliary tuberculosis in a child 8 months of age, diligent search of many sections failed to disclose the presence of lymphoid areas in the face of the presence of a distinctly local

infectious process of acknowledged chronic type.

Another case in point is our failure to find these areas after exhaustive search of many sections in a necropsy case of generalized tuberculosis in an adult even though a definite tuberculous process was demonstrated in the thyroid. Hellwig also believes that lymphocytic infiltration is the result of a purely local response, inflammatory in nature, but the number of his cases is small and he offers no assurance of exhaustive search for areas of lymphoid tissue. We have repeatedly called attention to the necessity of many blocks and intense study. We feel that the discrepancies occurring in our work are largely due to this factor. Figure 3 shows a small area of lymphoid tissue in a gland with extensive epithelial hypertrophy in all sections. This was the only area of lymphatic tissue found, however, in sections from many blocks. Furthermore, it is not our experience that with these areas epithelial hypertrophy always co-exists. We have seen many cases in which no epithelial hypertrophy and but an occasional area of lymphoid tissue could be demonstrated in sections from many blocks. In one instance only a single area of lymphoid tissue was found in sections from nine different blocks, none of which showed hypertrophy of the epithelium. We fully agree with Warthin that epithelial hypertrophy persists longer in and about the lymphoid tissue in the face of iodinization and feel that this is the proper interpretation when the two processes are found to be co-existent. These observations, in our opinion, indicate that the production of rudimentary lymph nodes does not form a part of the picture in inflammatory processes in

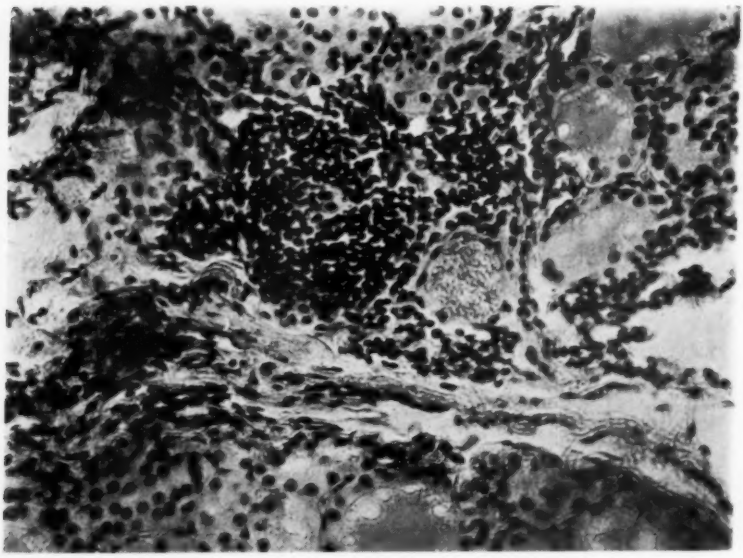

FIG. 3. Photomicrograph showing the only area of lymphoid tissue found in numerous sections from a gland showing extensive epithelial hypertrophy.

the thyroid gland and that the lesion in question is not of inflammatory origin.

The almost universal presence of this lesion in surgical thyroids from patients exhibiting clinical Graves' disease is the main point of interest in the entire work, since Warthin's interpretation of lymphocytic areas as a diagnostic criterion is strongly supported. To us, there is a difference in the amount of lymphatic tissue and the degree of its hyperplasia, depending on the severity of the toxic symptoms of the patient and the degree of clinical response to iodine treatment. Figure 4 is a photomicrograph of a specimen from a patient whose basal metabolic rate, before iodine treatment, was + 43, improvement under iodine was very slight, the basal rate remained high and partial resection of the gland was of but slight clinical benefit. Later a nearly total extirpation was considered necessary. The microscopical picture of the two specimens of thyroid gland were essentially identical, though nearly two months elapsed between the two resections. Lymphatic nodules were numerous throughout all sections and epithelial hypertrophy is persistent, particularly adjacent to the lymphatic tissue. On the other hand figure 5 is from a case with a few symptoms, basal rate of + 21, and showing microscopically but an occasional area of lymphatic tissue, though many blocks were examined. While we have several such comparative instances we realize that definite conclusions would necessitate a painstaking study of a great number of cases with carefully taken histories. We have also observed that in those cases of infant and selected necropsy glands showing lymphatic tissue, definite

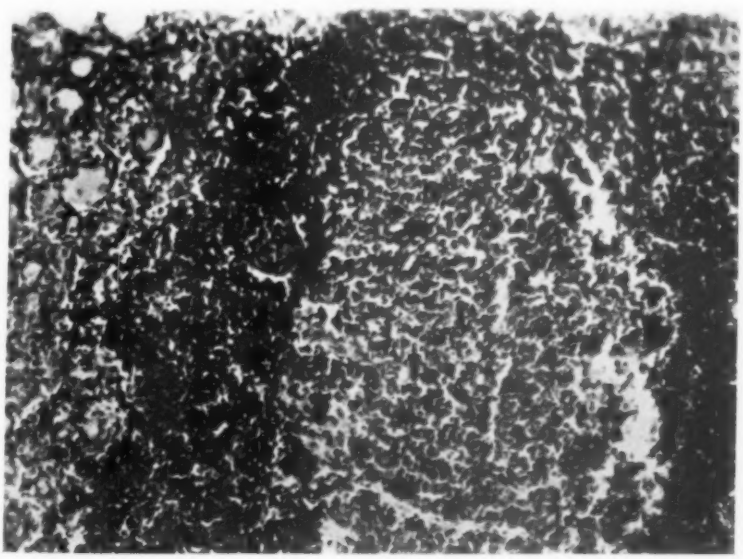

FIG. 4. The marked development of lymphoid tissue in the thyroid of a severe case of exophthalmic goiter.

hyperplasia is lacking, the tissue not showing very distinct germ centers. (Figure 6.) Continuing this line of reasoning it would follow that symptoms of Graves' disease manifest themselves only when these congenital areas become hyperplastic and further, that the more extensive the hyperplasia the more severe are the symptoms. As said before it is our observation, as well as Sager's, that these areas persist in the face of evident adequate iodine therapy. We do not know, however, that they are not reduced in number, size and degree of hyperplasia. Reinhoff, who has studied glands before and after involution makes the statement that "The areas of lymphocytosis were much less frequent during and after involution and the areas that were present seemed to be markedly reduced in size". One must recall however, that this observation is based upon seven specimens only. The futility of too enthusiastic generalization on so limited a number of cases is too obvious to require comment. Warthin also considers them to be affected when iodine treatment is first instituted, but that they later become increased in size. From this, one might be led to conclude that the transitory or partial benefit derived from iodine is in halting further hyperplastic processes in the lymphoid tissue as well as in the epithelial elements of the gland. We have previously called attention to the fact that the use of iodine as a therapeutic agent oftentimes so changes the appearance of the gland of exophthalmic goiter as to make the recognition of a definite pathological process next to impossible were one to consider the epithelial elements only. While there is no question in our mind regarding the definite pathology exhibited by the thyroid epithelium, we are forced by our own

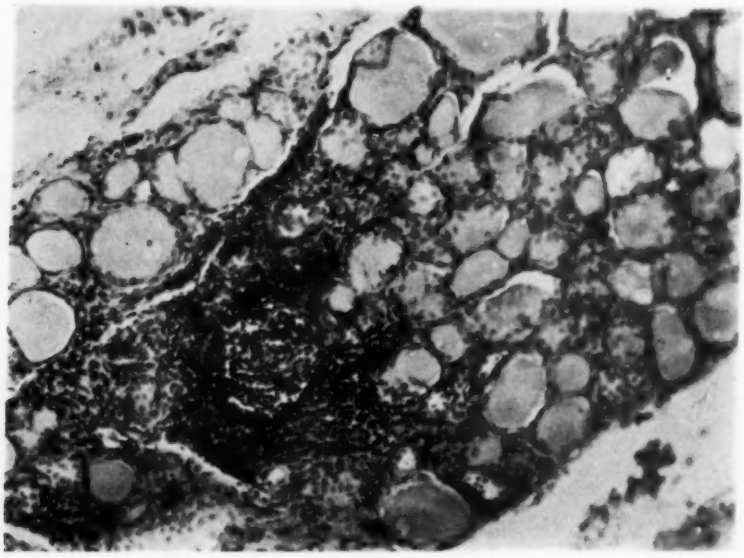

FIG. 5. Lymphoid tissue in a mild case of exophthalmic goiter.

experience as well as by the evidence presented in the literature, to recognize its instability as a pathognomic lesion of Graves' disease in the presence of iodine treatment.

We have shown a remarkably close agreement in the clinical diagnosis and the pathological picture when the presence of lymphatic tissue was considered an essential lesion of Graves' disease. Were this lesion to be ignored and the conclusions drawn only from the epithelial hyperplasia and hypertrophy exhibited, a regrettably poor agreement between clinical and pathological findings would result. The presence of lymphatic tissue in practically all glands removed surgically from patients exhibiting undoubted clinical signs of the Graves' syndrome, forces one to consider it a lesion of this disease. We feel that the few cases in which the lesion was not demonstrated represent clinical diagnostic errors or cases in which the lesion was missed because of insufficient search. In this respect this lesion can be compared to infiltrating malignant cells in the prostate, for instance, where it is oftentimes necessary to section many blocks before carcinomatous areas can be found. Certainly, failure to demonstrate these areas of lymphatic tissue in a few blocks does not warrant a conclusion that they are not present in other portions of the gland. Their persistence after iodine medication confers upon them a major rôle as a diagnostic lesion inasmuch as we have shown them to be a much more trustworthy indication of hypertrophic and hyperplastic processes than changes in the epithelium.

In the course of a study such as this, one is impressed by the futility of attempting the solution of many of the questions involved by drawing conclusions from a study of dead pathol-

FIG. 6. A small area of lymphoid tissue in the thyroid gland of an infant.

ogy. The problems involved, which are necessary of solution for a clear understanding of thyroid disease, must, in our opinion, be attacked by experimental methods for any reasonable hope of success. Such methods are yet to be devised.

Classification of Thyroid Disease

There are many classifications of thyroid disease suggested in the literature, few of which permit both clinical and pathological application. Menne *et al.* have proposed perhaps the most extensive workable classification, although it does not coincide with our view that there exists but one process involved in hyperthyroidism, that symbolized by the clinical syndrome of Graves' disease. Warthin proposed a simple classification as follows:

"1. Simple colloid goiter without Graves' constitution;
2. Nodular colloid goiter without Graves' constitution;
3. Simple adenoma with Graves' constitution;
4. Exophthalmic goiter (Graves' constitution);
5. Adenoma with Graves' constitution (so-called toxic adenoma)."

This classification is applicable clinically and is based on the presence or absence of the "Graves' constitution". It recognizes and emphasizes the adenomata in a manner that is to us confusing and not warranted, since it is our contention that the presence of adenomatous areas has no significance in hyperthyroidism. As has been often stated, no classification of any disease is of value that cannot be of clinical as well as pathological application. If the symptoms exhibited by the patient, be they ascribed to Graves' disease, hyperthyroidism, toxic adenoma, or what not, fit a given syndrome, and there is a constant pathological lesion, one is warranted in assuming the unity of the process. In view of the findings in our study, the practically universal presence of the lesion described as lymphoid hyperplasia, we suggest the following classification and diagnostic scheme.

1. Hypertrophic-lymphoid goiter—Graves' disease.
   1. Epithelial hypertrophy in non-iodized gland.
   2. Lymphoid hyperplasia.
   3. If iodized.
      1. Stroma increased.
      2. Colloid increased, thin and watery.
      3. Epithelial hypertrophy may be patchy or lacking.
2. Nodular colloid goiter.
   1. Large vesicles containing colloid occurring in pseudo-encapsulated areas.
   2. No lymphoid tissue or epithelial hypertrophy.
   3. May show degenerating colloid cysts.
3. Simple colloid goiter.
   1. Large vesicles, comparatively uniform.
   2. No lymphoid tissue or epithelial hypertrophy.
   3. May show degeneration, cysts, calcification.
4. Normal thyroid with adenomata.
   1. Encapsulated areas of "fetal"-like acini or
   2. Areas of more developed adenoma.
5. Inflammatory processes.
   1. Definite pyogenic infections.
   2. Tuberculosis, etc.
6. Malignant new growths.

If any thyroid would otherwise fall in the last five groups it will be seen that the presence of lymphoid tissue necessitates placing it in group 1. All the groups become modified by iodinization and all may contain adenomatous areas, and in addition there will be the rare specimen usually obtained at necropsy from the potential Graves' patient which will present small areas of lymphoid tissue. These latter cases must necessarily be considered as potential exophthalmic goiter in the absence of clinical signs.

Conclusions

1. It has been shown that areas of lymphatic tissue occur in the thyroid gland in 2.8 per cent of infants.

2. This tissue is also found in 2 per cent of thyroids from patients dying from diseases or accidents not involving the thyroid gland.

3. Areas of lymphatic tissue occur in practically all thyroid glands removed surgically from cases of undoubted Graves' disease.

4. The lesion described is not the result of a local inflammatory reaction.

5. The presence of lymphatic tissue in infant and selected necropsy specimens supports Warthin's contention of the existence of a "Graves' constitution", that exophthalmic goiter is the clinical manifestation of a congenital constitutional anomaly.

6. Warthin's conclusion that this lesion is diagnostic for Graves' disease is vigorously supported.

7. Adenomata have no causal relationship to the symptoms of thyriod disease since they occur with equal frequency in normal and pathological glands. The use of the term should be abandoned in connection with the clinical diagnosis of hyperthyroidism.

8. A simple classification and diagnostic scheme of thyroid disease that is clinically and pathologically compatible is suggested.

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Pulmonary Lesions in Human Tularemia*†

Pathologic Review and Report of a Fatal Case

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ALTHOUGH it is well known that tularemia is a blood-borne infection, little notice has been taken of the frequency with which it attacks the lung. Francis[1] reported abstracts of the twenty-four fatal human cases of which he had record up to October, 1928, and in more than one-third of these a diagnosis of intercurrent bronchopneumonia had been made. Simpson[2] subsequently expressed the opinion that the physical signs in many of these so-called bronchopneumonias were probably due to multiple tularemic necroses. The author[3] has recently published the thirteen cases which have come under his personal observation and six of these gave clinical evidence of intrathoracic disease (i.e.: pleural effusion, 2; bronchopneumonia, 2; bronchitis, 1; lung abscess, 1).

It seems more than a coincidence that each of the eight cases in which the chest was examined at necropsy should have shown some abnormality of the lungs or pleura. Death in these occurred from four days to five months after the tularemic infection. Simpson[2] reported "two lesions in the right lung, which were unquestionably tularemic focal necroses". Palmer and Hansmann[4] found "an inconsiderable amount of bronchopneumonia which did not give any clinical symptoms". Bardon and Berdez[5] reproduced a photograph showing tularemic nodules on the visceral pleura of their case and said "both lungs showed an extensive bronchopneumonia". Bunker and Smith[6] removed twenty-eight ounces of a deep straw colored fluid from the right thorax at necropsy and made a diagnosis of "coagulative necrosis of the right lung". Goodpasture and House[7] withdraw 200 c.c. of fluid from the left chest postmortem but were unable to find evidence of intrapulmonary damage. Verbrycke's case[8] had about 100 c.c. of fluid in each pleural space and "multiple areas of caseous necrosis averaging a hickory nut in size" in the lungs. Francis and Callender[9] quoted a case of Bruecken's dying five months after infection, in which "a calcareous area at the left apex was traced to a multilocular single cavity one centimeter in diameter".

In February, 1931, Massee[10] reported finding physical signs of pneumonia at the bases of both lungs in a case of tularemia dying on the eighteenth day of the disease. At necropsy, gross examination revealed areas of "late red hepatization" in both lungs which were

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†Received from publication, August 3, 1931.

interpreted as representing a "bronchopneumonia of the confluent type". Numerous short gram-negative bacilli, morphologically consistent with *B. tularense,* were seen imbedded in the tissue sections. Material from the lung was scratched into the skin of the abdomen of a guinea pig; a granulomatous ulcer developed from which *B. tularense* was cultured. This case shows that bronchopneumonia may be a manifestation of tularemia rather than a complication of it.

Many writers have remarked on the great similarity of the microscopic pictures seen in the tubercle of tuberculosis and in the caseous necrosis of tularemia, although the comparison has been made mostly in tissues other than the lung. Since the fundamental lesion in both is initially a small area of caseation, this resemblance is not remarkable. It seems peculiar that so little attention has been paid to the similarity of the clinical effects which may be produced by *B. tuberculosis* and *B. tularense.* Bronchopneumonia, pleural effusion, lung cavitation and lung abscess formation are at least some of the clinical conditions which may be caused by both organisms. One wonders if perhaps a few cases of tularemia have not been mistakenly diagnosed as tuberculosis.

Reference to the microscopic pulmonary lesions in human tularemia are scarce. Simpson[11] in his recent monograph on the disease discusses this phase briefly: "Foci of caseous necrosis with peripheral epithelioid and fibroblastic proliferations also characterize the hepatic and pulmonary lesions". Stitt[12] paraphrases Francis' description as follows: "The lungs present small necrotic foci or white plaques on the pleura; they contain focal necroses, or there may be bronchopneumonia of any degree, even to the involvement of almost an entire lobe; the alveolar walls are infiltrated with edema and large mononuclears, and the alveolar contents consist of a few leucocytes and red blood cells and a small amount of fibrin". At this time, the criteria for making the diagnosis of tularemia of the lung from pathologic studies alone seem indefinite: further work is necessary along this line.

The following case is presented because few fatal cases of tularemia have been reported. The pulmonary lesions described are sufficiently similar microscopically to the other cases reported to deduce that the changes in the lungs in this case were due to tularemia. It is felt, however, that they are also sufficiently different to be of especial interest.

Report of Case

History. A negro, aged 38, was sent to the hospital on Dec. 6, 1928, from Culpeper, Va. At the time of admission the patient gave an unreliable history but the following facts were supplied by his family physician, Dr. J. W. Humphries:

On Nov. 4, 1928, the patient, who had had no contact with rabbits during the preceding six months, skinned an opossum found dead in a cage with several live opossums. Four days later his physician was called because of the sudden onset of chills, fever, generalized aching and prostration. The temperature was 102° F. It was observed that the patient's hands "were considerably chapped" although no ulceration was noted. On Nov. 11, when the physician called again, the temperature was 103° F. and "a suppurative condition around four badly broken front teeth had developed". There was swelling of the glands of the neck. On Nov. 16, at the advice of his physician, two of these teeth were extracted under local anesthesia and a "large amount of pus was evacuated". The patient was

able to sit up during the following twenty-four hours, but, on Nov. 17, was again forced to bed. On this date, a specimen of blood was sent to the Virginia State Board of Health Laboratory for Widal agglutination and was reported negative. In accordance with their custom of testing all Widal-negative serums with *B. abortus* and *B. tularense*, these additional agglutinations were done. The *B. abortus* agglutination was negative but the agglutination with *B. tularense* was reported "positive in dilution of 1:40". The agglutination was repeated with a specimen of serum obtained on Dec. 3 and was positive with *B. tularense*, 1:5120. The same serum tested by the U. S. Hygienic Laboratory agglutinated in dilution of 1:1280.

On Dec. 6, the patient was admitted to the hospital, mainly on account of cough which had developed about two weeks previously. The cough was productive of abundant foul, bloody sputum and was becoming progressively worse.

Examination. The patient was emaciated, obviously ill, sweating profusely, and apparently in stupor. There were many carious teeth with marked pyorrhea and receding gums, and cavities of the two recent extractions. The left axillary glands were slightly enlarged but not tender. The other glands were normal. In spite of a careful search, no ulceration of the skin and no scars were found. There was an old crushed fingernail on the left third finger. The physical signs in the chest indicated fluid or consolidation, or both, in the right lower lobe. Routine examination was otherwise normal. Rectal temperature was 105° F., pulse 120, respiration 32. The blood pressure was 128 systolic, 84 diastolic. Urinalysis was essentially negative. Hemoglobin was 53 per cent (Dare); red blood cells numbered 2,710,000; white blood cells 8,200. The blood smear was typical of secondary anemia and the differential count was: 79 per cent polymorphonuclears, 21 per cent lymphocytes. The serum agglutinated *B. tularense* strongly in dilutions of 1:800 and gave an incomplete reaction in dilution of 1:1600. It did not agglutinate *B. typhosus* or *B. abortus*. The blood Wassermann reaction was negative. The sputum was composed of reddish-brown, bloody, mucopurulent material; no acid fast or Vincent's organisms were found in six examinations.

Course. The patient remained toxic and at times irrational. His temperature was of the septic type, ranging from normal to 105° F. He coughed up foul bloody sputum, filling one or two sputum cups a day. On Dec. 8, an attempt at thoracentesis was unsuccessful. On the 10th, a single bedside chest plate (figure 1) was reported as follows: "The lower half of the right chest shows a marked increase in density which is honeycombed with large irregular areas of decreased density; these have fairly definite borders. The largest of these areas of rarefaction is 6 by 3 cm. and occupies the space between the sternal ends of the second and fourth ribs. The appearance on the left is that of rather heavy hilus shadows. This region is also thickly studded with small round areas of calcium deposit.

Conclusions: Lung abscesses, right; probable bronchiectasis, left." The patient continued to become more toxic and died from general toxemia on Dec. 15, 1928.

Necropsy. Examination was performed three hours after death by Drs. Harry T. Marshall and Joseph B. Graham.

The pleural cavities contained no fluid. The anterior aspect of the right lung was normal. The middle lobe was adherent to the upper lobe and partially so to the lower. Posteriorly the lung was bound down by extensive and firm adhesions at the base. On removing the right lung a cavity was encountered where the lung had been attached. This cavity was 8 by 12 cm. and extended from the diaphragm to within a centimeter of the top of the lower lobe. It seemed as if the anterior wall was formed by rough, irregular, dirty gray, necrotic lung tissue, and the posterior wall by the visceral pleura which was adherent to the chest wall. This cavity contained about a pint of foul, purulent, bloody fluid. A probe passed down the main bronchus failed to communicate with this cavity. On section a large friable thrombus was found almost obstructing the lumen of the right pulmonary artery; numerous thrombosed arterioles were seen.

The left lung was congested in spots but elsewhere was pale. It was somewhat emphysematous. A slightly darker region occurred in the upper lobe; the pleura was lit-

tle involved over this area. A thrombus was found partially filling the pulmonary artery at the hilus. The outer wall of the thrombus was more pliable and the center was softer than in the right lung. Section through the consolidated area showed multiple thrombi.

In the angle of the bifurcation of the trachea there was a walnut sized mass of lymph nodes, which were coherent, soft and under tension. On section, there was much pigment deposit and three or four very small pearly spots which did not project above the surface.

The pericardium and heart appeared grossly normal except for a cloudy swelling of the myocardium. Both the spleen and liver failed to reveal any lesions suggestive of tularemia either on the surface or on section. The liver was of the fatty, nutmeg variety and the spleen resembled an acute splenic tumor of the septicemic type. The kidneys were cloudy and congested. The other viscera were normal.

Histologic Study. The microscopic sections were studied by Dr. Thelma Brumfield, who had at her disposal material loaned by Dr. Edward Francis from two of the cases reported by Francis and Callender. After a comparison of these with those from this case, Dr. Brumfield felt justified in saying that the lesions in this case were due to tularemia. The significant features were found in the sections from the axillary and bronchial lymph nodes, the lungs and the liver. Dr. Brumfield's reports on these are quoted in detail:

"Left Axillary Lymph Node: In this section were two small areas with a central coagulative necrosis, surrounded by large mononuclear epithelioid cells and a zone of fibroblasts. No Langhans cells were seen but these two areas closely resembled tubercles. The germinal centers from other areas of this node were pale and the sinusoids contained numerous large mononuclear cells. Eosinophils were relatively abundant. Another section contained no necrotic areas and no other unusual changes except hyaline degeneration of small blood vessels.

"Hilus Lymph Nodes: There were three areas of coagulative necrosis similar to those already described except that they lacked such definite zones of epithelioid and fibroblastic cells. The other lymph nodes examined were apparently normal.

"Right Lung: One section revealed in a medium sized artery an occluding thrombus containing many clearly outlined red blood cells. This appeared to be a propagated

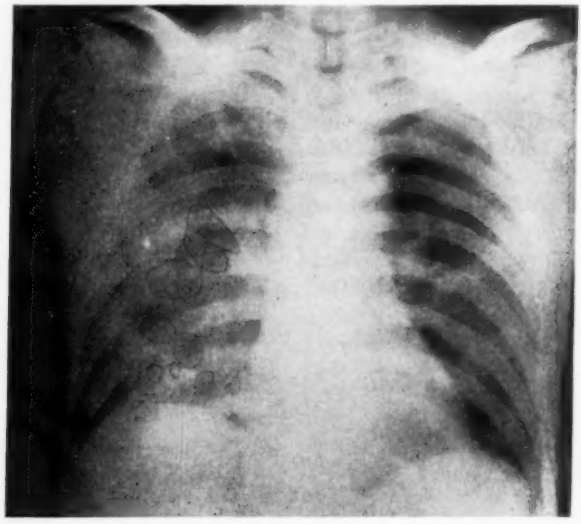

FIG. 1. Retouched bedside film taken December 10, 1928, showing cavities in right lung.

thrombus though it seemed to be partially attached to the vessel wall. In the adventitial tissue surrounding, there was a striking accumulation of mononuclear cells and a proliferation of fibroblasts in which were a few well preserved polymorphonuclear cells. The smaller vessels of this area were congested with red blood cells. Just outside the adventitial tissue the alveoli contained many large mononuclear cells. In this area there were a few spaces containing semi-necrotic exudate, composed chiefly of mononuclear cells and some polymorphonuclears. The remainder of this section showed a diffuse widespread necrosis of the lung tissue. This resembled closely a caseous pneumonia, since within the necrotic alveolar exudate were still retained the outlines of large mononuclear cells without pus formation, and only a moderate degree of hemorrhage. Gram-Weigert stain was negative for organisms in this tissue. Another section, adjacent to the large abscess cavity, contained a few air-bearing alveoli with thickened walls, and numerous microscopic nodules of consolidated lung tissue, the centers of which were necrotic, resembling early tubercles and surrounded by epithelioid cells and collagen fibers. In the same section was an area of profuse hemorrhage into the lung tissue in which appeared numerous areas of coagulative necrosis. Histologic details here were obscured by the hemorrhage. Gram-Weigert stain was negative.

"Other sections from the wall of the abscess showed marked proliferation of fibroblasts with collagen production, thick walled vessels, and an exudate of mononuclear and polymorphonuclear cells. Several small arteries revealed a proliferative endarteritis.

"Two minute areas of necrosis surrounded by large mononuclear cells were seen in the sections from the liver."

Summary

The reported effects of *B. tularense* on the human lung are reviewed and attention is called to the probable frequency and importance of these pulmonary manifestations. A case with necropsy is presented with the following observations of interest: (a) the probable source of infection was an opossum, (b) the clinical diagnosis of pyogenic lung abscess was discredited by microscopic study of the tissue, (c) the pulmonary damage was extensive and of prime importance as a cause of death, (d) the multiple pulmonic thrombi, with attending areas of necrosis were probably attributable to the tularemic infection, and (e) gross caseous nodules were lacking in the liver and spleen.

Two additional reports [13, 14] of pulmonary lesions in human tularemia have appeared since this paper was written.

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Oliver Goldsmith, M.D.*

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WITH no other medical poet is the dignified doctoral prefix more commonly employed. He was "Dr. Goldsmith" to Boswell and the Johnson circle, and his contemporaries almost without exception referred to him as the "Doctor" yet the medical side of Goldsmith's life has been rather neglected, though it is both a considerable and interesting subject. The circumstances of his medical education, his attempts to practice in Southwark and in London, his relation to one of the celebrated nostrums of the day, and its use in his last illness are all well attested though not commonly known facts.

His biographers are unable to decide with certainty whether Oliver Goldsmith was born in the village of Pallas or the village of Elphin, Roscommon, Ireland. The year of his birth is also in doubt, though it was probably 1728. This is the date inscribed in the tablet in Westminster Abbey. Curiously enough the day of his birth, November 10, is the best authenticated of these three facts regarding the place and time of his appearance in the world. His father, the Reverend Charles Goldsmith, was a poor country curate. His son has immortalized his kindly and guileless character in the "Vicar of Wakefield" and he was also the original of the clergyman of the "Deserted Village", "passing rich on forty pounds a year".

When Oliver was seven years of age his father's circumstances were improved by the gift of the living at Kilkenny West, and the family moved to the parsonage on the outskirts of the pretty little village of Lissoy not far from Athlone. Lissoy is celebrated as the "Sweet Auburn, loveliest village of the plain" and its rural beauties are pictured in the opening lines of the "Deserted Village".

Goldsmith attended the school at Lissoy kept by an old pensioned soldier, full of stories of Marlborough's wars and the whimsical legends of Celtic Ireland. He must have influenced the imaginative mind of the boy destined to be one of the greatest of English poets. There was little in Oliver's appearance however to indicate a brilliant future. He was homely to the point of positive ugliness, awkward, loose jointed and undersized. Smallpox, from which no one before the time of Jenner escaped, had further disfigured his countenance. A peculiar guilelessness and simplicity of character was an additional incitement to making him the target for all sorts of ridicule.

* Received for publication, October 12, 1931.

At seventeen he was packed off to Trinity College, Dublin, where he was entered as a sizar or poor student. On one side of the entrance gate fronting on College Green, Trinity has erected a noble statue to this poor sizar who was to be considered by the world as one of her most famous sons, no small distinction as Trinity was also the Alma Mater of Edmund Burke, Dean Swift, Bishop Berkeley, and Thomas Moore.

Goldsmith's college career was rather stormy. He was one of those good hearted, good natured, heedless persons, easily led, and loving gayety and conviviality. Once he was expelled for participating in a riotous party within the precincts of the college. His scholarship, too, does not seem to have been very remarkable but he was finally graduated on February 27, 1749, O.S., with the degree of Bachelor of Arts. The next three of four years were spent in fixing upon a profession. He attempted to take holy orders but was rejected by the Bishop; some say because of failure to pass the requisite examination, others because he presented himself to the Bishop arrayed in scarlet breeches. It was decided that he should study law and he was equipped with a new outfit of clothes, a good horse and thirty pounds. In a few months he returned with a single rusty suit, a broken down pony, and one shilling. He now lived for a time with his indulgent uncle Contarine, and made good progress in learning to play the flute and fiddle and in writing verses, accomplishments that pleased his uncle and a pretty cousin, but did not help him in securing an honorable or independent position in the world.

Most of the Goldsmith family were poor and improvident. There was one notable exception. This was Dean Goldsmith who was the incumbent of a rich deanery and whose position and material wealth made him an oracle to his poor relatives. He appears to have asked: "Why not make Oliver a physician?"

The suggestion of a great man like the Dean could not be disregarded and in the Autumn, of 1752, Oliver was entered at the University of Edinburgh as a "Student in Physic" to use his own words. As a medical student he had an experience in respect to his first boarding house that all other indigent medical students will appreciate. The table was furnished like that of Don Quixote, whose weekly menu consisted of "Soup composed of somewhat more mutton than beef, the fragments served up cold on most nights, lentils on Fridays, stew on Saturdays, and a pigeon by way of addition on Sundays". The similarity of this diet to that of Goldsmith's boarding house is shown by his description of what could be done to extend a loin of mutton throughout the week. "A brandered chop was served up one day, a fried steak another, collops with onion sauce a third, and so on until the fleshy parts were quite consumed when finally a dish of broth was manufactured from the bones on the seventh day, and the landlady rested from her labors."

He spent two winters in Edinburgh where he made a better reputation as a story teller and good fellow than as a student. However, he took a particular interest in chemistry and had for his professor, Joseph Black, the discoverer of carbonic acid gas, who remembered Goldsmith as a promising pupil. Another of his teachers was

Alexander Monro, senior, the celebrated anatomist.

Goldsmith's fondness for dress and his vanity have been frequently noted. A tailor's account, while he was a medical student, is full of rich colors and fabrics. "To 2½ yds. Sky-Blew satin, at twelve shillings a yard; To ¾ yds. fine Sky-Blew Shallon, 1 s. yd.; To a fine small hat 14 s.; To 1 oz. 6¾ dr. silver hat lace, 8 s.; to a pair fine thd. black hose; to 3½ yds. best fine high claret colored cloth, 19 s." So Goldsmith was not illy dressed during this period and furthermore the tailor's ledgers show that he paid his bill.

Although the University of Edinburgh was, and is today, one of the most famous medical schools of the world, Goldsmith quitted it after two years to make a tour of the Continent. In a letter to his good natured uncle Contarine, who financed him to some

Fig. 1. Oliver Goldsmith, M.D.

degree in his medical studies, he says: "I intend to visit Paris where the great Monceau instructs his pupils in all the branches of medicine and the next winter go to Leyden. The great Albinus is still alive there and 'twill be proper to go through only to have it said that we have studied in so famous a University."

Goldsmith's real reason for going abroad was no doubt his desire to see the Continent. Edinburgh was scarcely less celebrated as a medical school than Leyden, yet he well describes the advantages that take the student to another country to carry on the same studies as at home. To be able to say that one has been at a famous foreign University, the professional contacts in other lands and cities, the experiences of travel are valuable acquisitions not to be obtained in any other way, and the world takes note of these things and the returning student finds that he has an added prestige not possessed by the stay-at-home classmate.

In February, 1754, Goldsmith took up his studies at Leyden and no doubt attended the lectures of Albinus, one of the greatest of anatomists and professor at Leyden for more than fifty years. It is pretty evident, however, from certain descriptions he has given of the fair sex both at home and abroad that his studies were not all of a professional character. In one of his letters to his uncle Contarine he compares the Dutch and Scottish types of femininity. "The Dutch woman and a Scotch will bear comparison. The one is pale and fat, the other lean and ruddy; the one walks as if she were straddling after a go-cart, and the other takes too masculine a stride. I shall not endeavor however to deprive either country of its share of beauty."

He had arrived in Holland with 33 pounds sterling and borrowed money from another Irish student, Ellis, afterwards a physician of some note, when he left Leyden and began his travels through France, Switzerland, and Italy. According to his own account much of the journey was on foot and he often stayed at the houses of peasants, paying for food and lodging by playing the flute or telling amusing stories of his adventures. The journey was begun in 1758 and lasted about one year. During it he visited Louvain, Paris, and Padua. It was from the University of Louvain that he is supposed to have received the degree of Bachelor of Medicine, a title first used in connection with his name in 1763, when it is appended to one of the Dodsley agreements. Many of the records of Louvain University were destroyed during the French Revolution so that documentary evidence was not available when Prior and Washington Irving attempted to examine into this subject. Macauley expresses his doubts that Goldsmith ever obtained a medical degree, and indeed intimates that, like all travelers, he drew the long bow pretty generally. Goldsmith himself tells of having seen Voltaire in Paris and describes a conversation with him in most circumstantial terms, though it is now known that Voltaire was not at the time within a hundred leagues of Paris so that Macauley's doubts are not ill founded. Though the question of the medical degree from Louvain cannot be settled other than by a Scotch verdict of "not proved", the general use of the title of "Doctor", Goldsmith's use of the term "Bachelor

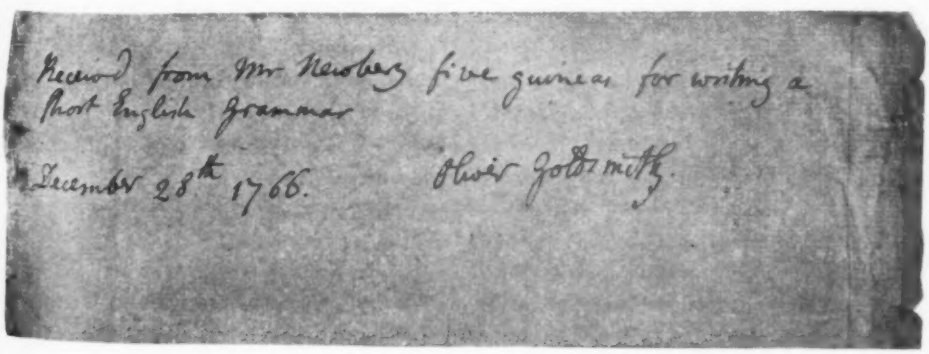
of Medicine", and his claim that this degree was received from Louvain must carry weight.

Goldsmith returned to England in 1756, penniless and friendless. His uncle Contarine, who had been his patron and who had interested himself in his nephew's behalf on all occasions, was dead. For a time his circumstances were desperate. He slept in the streets and consorted with beggars. He attempted unsuccessfully to obtain employment in an apothecary shop. He did however obtain a place as usher in a private school but left it to become the assistant of a chemist. There, through the assistance of a fellow student at Edinburgh, Dr. Sleigh, he commenced the practice of medicine at Bankside, Southwark. He starved here, too, though he told another old college companion, Beatty, who met him at this time, that "He was practising Physic and doing well". Dr. Farr, who had also been with him as a medical student, says that when he met Goldsmith at this time the poet was clothed in a coat of rusty black velvet with a patch over the left breast, an evidence of poverty that he concealed by holding his three-cornered hat over it.

Dr. Sleigh introduced Goldsmith to Richardson, the novelist and bookseller, who gave him some literary hack work to do and it was thus that he began his career as a man of letters. His work soon attracted the attention of Dr. Samuel Johnson and through his friendship Goldsmith became a member of the famous literary club, the record of whose meetings has been so completely reported by Boswell. It is of interest that two of the original members of the club were medical men for, in addition to Goldsmith, the membership included Dr. Nugent, the father-in-law of Edmund Burke, a Roman Catholic, and a successful and highly respected physician.

Both Johnson and Sir Joshua Reynolds recognized Goldsmith's genius. Hawkins says that he was looked at askance by some of the other members "as a mere literary drudge equal to the tasks of compiling and translating but little capable of original and still less of practical composition".

This view was changed by the publication of "The Traveler" and the "Vicar of Wakefield". The former has been declared with good reason to be the finest poem in English since the appearance of Pope's "Essay on Man"


Received from Mr Newbery five guineas for writing a short English grammar

December 28th 1766. Oliver Goldsmith

FIG. 2. An autograph receipt by Oliver Goldsmith, M.D.

and the excellence of the "Vicar of Wakefield" has been attested by successive generations of readers.

The years that followed were probably the most successful and happy of Goldsmith's life. He enjoyed the praise of "The Traveler" and the "Vicar", and the admiration excited by "The Deserted Village", perhaps the finest pastoral poem in English. These years also saw his success as a playwright with the comedies of "She Stoops To Conquer" and "The Good Natured Man".

He was frequently the guest of Reynolds, Mrs. Thrale and Mrs. Vesey. The given name of Mrs. Vesey's husband was Agronisham and we can gain some idea of the fame of the Johnson circle at this time when we find that Agronisham Vesey, though wealthy and socially prominent, was so concerned over his entrance into the Literary Club that the night his name came up for discussion he had a relay of foot messengers to bring the news of his election and was much agitated until he found that he had been accepted for membership. At Sir Joshua Reynold's, Goldsmith met the Hornecks and fell in love with the younger daughter celebrated as the "Jessamy Bride". His financial affairs, though always in a tangled state due to his improvidence, were nevertheless better than at any other time in his career and he appears to have enjoyed an income of four or five hundred pounds a year. This is the time of the "bloom-colored coat" mentioned by Boswell.

Three features of Goldsmith's medical life should be noted. The first of these was his attempt to gain a medical appointment in India. This attempt was successful and he was appointed physician and surgeon to one of the factories of the East India Company on the Coromandel Coast. The appointment was worth fifteen hundred pounds a year, a very large sum for those days, partly in salary and partly in fees and perquisites. It was necessary that he pass a professional examination and make a deposit toward his passage money before he was finally accepted for the post. He probably failed in one of these requirements for he was never actually appointed and none of his friends could learn from him the real reason for the final failure of the scheme.

Goldsmith had always a great interest in the Orient and in 1761 he drew up a memorial to Lord Bute in which he suggested a scientific mission to Aleppo, of which Goldsmith was to be the head, to inquire into the useful arts, inventions, and customs of the East with the idea of bringing back to Europe methods unknown there. The Government paid no attention to the memorial except to disapprove it. No one could have been more unsuited than Goldsmith to lead such an expedition as Dr. Johnson pointed out in one of his characteristic pronouncements: "Of all men" said he, "Goldsmith is the most unfit to go upon such an inquiry. Sir, he would bring home a grinding barrow, which you see in every street in London, and think that he had furnished a wonderful improvement."

After the failure of his India appointment, he sought to be examined for a surgeon's mate in the Army. Records of the College of Surgeons showed that he appeared for examination at Surgeon's Hall, December 21, 1758, and was found *not* qualified.

In spite of this, in 1765 after the

publication of "The Traveler" his social and financial prospects were much changed for the better, and Sir Joshua Reynolds, always Goldsmith's sincere well wisher urged him to resume the practice of medicine and pointed out the advantages he could obtain from being known as the member of such a profession. It must be remembered that in eighteenth century England the social position of the physician was high, the large number of men of family and talent from Harvey and Sydenham to Meade, Garth and Arbuthnot in the medical fraternity having done much to bring it to a high plane. Goldsmith therefore took his friends advice and began again as a medical practitioner under more favorable circumstances than surrounded him in his first attempt. He was now a man of note in the world of letters, had many powerful friends, and was no longer pressed for funds. In spite of these advantages his practice did not flourish as he himself quickly tired of the restraints and responsibilities imposed by his profession. Most of his patients were among those who forgot to pay him and his fees in consequence did not come up to his expectations. Finally an apothecary questioned the dosage of a drug prescribed by Dr. Goldsmith, and in the dispute the patient, a Mrs. Sidebotham, sided with the pharmacist to the disgust of the Doctor who left the patient and practice in a passion. To Beauclerc he said, "I am determined to leave off prescribing for my friends". "Do so, my dear Doctor", answered the wit, "whenever you undertake to kill, let it be only your enemies."

Goldsmith's last illness and death were attended with circumstances that led to considerable controversy at the time. The poet had suffered in 1772 from an attack of dysuria which may have been due to an old Neisserian infection, though it may of course have been a non-specific condition. At this time he had been treated by Dr. James, a respectable physician of the day who was the author of a three volume Medical Dictionary, but is best known, however, by a secret prescription sold everywhere as "James' Powder". The sale of this powder made him rich. It was then common for remedies to be kept secret by reputable medical men so that his conduct was not as unethical as it would be considered today. The powder was a compound of calcium phosphate and antimony oxide, and was diaphoretic, emetic, or purgative in its action depending on the dose used. It survives now in the National Formulary as the pulvis antimonialis, or James' powder, where the dose is given as 0.2 gram or 3 grains. Goldsmith had used this remedy under James' direction with relief of his symptoms and had apparently conceived an exaggerated idea of its value. In the early part of 1774 he had an exacerbation of his cystitis and his general health seems to have been impaired. He became quite ill on March 25, and sent for Mr. Hawes whose account was published shortly after Goldsmith's death.

The following is the narrative of Mr. Hawes:

"On Friday, the 25th of March, at 11 o'clock at night, the late Dr. Goldsmith sent for me to his chambers. He complained of violent pain extending all over the forepart of his head; his tongue was moist; he had no cold

shiverings, or pain in any other part, and his pulse beat about 90 strokes in a minute. He then told me he had taken two ounces of ipecacuanha wine as a vomit, and it was his intention to take Dr. James' Fever Powder. I replied that, in my opinion, this was a medicine very improper at that time, and begged he would not think of it. But I am sorry to say that every argument used seemed to render him more determined in his opinion; which gave me much concern, as I could not avoid thinking that the man whom I had every reason in the world to esteem was about to take a step which might prove extremely injurious to him. I therefore endeavoured to reason medically with him and observed that his complaint appeared to be more a nervous affection than a febrile disease.... However, though I reasoned with him on the subject for near half an hour by his bed-side, and vehemently entreated him not to take Dr. James' Powders, yet I could not prevail upon him to say he would not. At least I addressed him, to the best of my remembrances in the following manner:

" 'Please, Sir, to observe, that if you do take the fever powder, it is entirely without my approbation; and, at the same time, remember how very anxious I have been to persuade you to desist from doing it, and now I will take my leave, if you will be kind enough to grant me one request.' He very warmly asked me what that was. I told him that, as he had always consulted Dr. Fordyce in preceding illness, and had expressed the greatest opinion of his abilities as a physician, I hoped he would permit me to send for him. It was full a quarter of an hour before I could obtain his consent to this, as the taking of Dr. James' powders appeared to be the only object which employed his attention; and even then he endeavoured to throw an obstacle in the way, by saying that Dr. Fordyce was gone to spend the evening in Gerrard Street, 'where', added he, 'I should also have been, if I had not been indisposed'."

Fordyce, an M.D. from Edinburgh in 1758 and a member of the Johnson circle, now took over the case but not until the poet had obtained from Hawes some James' powders which on taking he declared were not of proper composition and made him worse. He continued to grow worse, and became very drowsy and weak with a pulse ranging from 120 to 140 and an irregular low temperature.

On Sunday night, April 3, he fell into a deep sleep; at four o'clock in the morning of April 4, he was seized with a convulsion and expired an hour later.

His death was thus announced in the Public Advertiser of April 5: "Yesterday morning died, much and deservedly regretted, at his chambers in Brick Court, in the Temple, Dr. Oliver Goldsmith, author of the poems of the Traveler, and Deserted Village, and many ingenious works in prose. He was seized on Friday night with a nervous fever in his brain, which occasioned his death."

A considerable controversy arose as to what effect the popularly used James' Powder had on the course of his illness, some declaring that it had hastened his end, others defending it. A rumor arose that Dr. Goldsmith believed that there had been a mistake in the compounding of the powder and this rumor became so troublesome that

Hawes published a brief account of the affair, apparently to defend himself against gossip.

Just what the exact diagnosis was is not known but it is clear that an infection of the genito-urinary tract was the basic condition and the injudicious use by the patient, against the advice of his medical attendant, of a powerful irritating emetic and purgative produced a gastro-enteritis as well. Hawes and, indeed, all the medical men who attended Goldsmith, appeared to have done all that was possible.

Hawes became a man of mark, was a friend of Reynolds and of Goldsmith and the fact that he managed the latters' affairs and disposed of his effects after the poet's death indicates that Goldsmith's friends did not consider him remiss in any important particular. Hawes was made a Doctor of Medicine in 1780. He died at his birthplace, Islington, in 1808.

Goldsmith's death excited very little attention among the public as a whole but there was a general mourning among all his friends and associates to whom his simplicity and kindness of heart greatly endeared him. If one were to attempt to convey an idea of this good natured friendliness in a single incident it could perhaps be best done by quoting the concluding line of one of his letters to a member of a country family. After asking that his respects and regards be given to the members of the family he adds: "And if there is an old dog in the family pat him on the head for me".

After Goldsmith's coffin had been closed it was opened again at the urgent request of the Jessamy Bride, the lovely Mary Horneck, that she might cut off a lock of his hair. This memento of the poet she treasured through her long life (she did not die until 1840) and the memory of her affection and devotion have in the words of Irving, "hung a poetical wreath above her grave".

Sympathy and kindness were nearly the only attributes that Goldsmith possessed that fitted him for the practice of medicine. In all other respects few could have been so unfitted by nature for so exacting a profession. He was careless and impatient of restraint, with little idea of responsibility. His knowledge was of a miscellaneous and impractical kind and he never seems to have been a serious student.

As both a poet and a prose writer Goldsmith holds a high place in English literature. His smooth and flowing prose is unsurpassed by any English writer, except Addison, and his graceful verse was distinguished in a literary age celebrated for the quality of its poetry.

A little known fact regarding Goldsmith is the influence his writings had upon the life and work of Goethe. This influence is to be distinctly seen in Goethe's thought and life and was acknowledged by him in terms that deserve to be repeated. He expressed it strongly in his autobiography and in 1830 when he was eighty-one years of age, in a letter to Zelter he said: "It is not to be described, the effect that Goldsmith's Vicar of Wakefield had upon me, just at the critical moment of mental development. That lofty and benevolent irony, that fair and indulgent view of all our infirmities and faults, that equanimity under all changes and chances, and the whole train of kindred virtues, whatever names they bear, proved my best edu-

cation; and in the end they are the thoughts and feelings which have reclaimed us from all the errors of life." Further he mentions that he has recently read "the charming book again from beginning to end." As Foster expresses it "The strength which can conquer circumstances; the happy wisdom of irony which elevates itself above every object, above fortune and misfortune, good and evil, death and life, and attains to the possession of a poetical world, first visited Goethe in the tone with which Goldsmith's tale is told."

Johnson, who at times had borne an almost parental relation to Goldsmith, scolding him for his shortcomings in the parental style, loved him and felt his death the most keenly of any of the warm circle of friends with the possible exception of Sir Joshua Reynolds. It was Johnson who composed the epitaph inscribed on a marble tablet beneath the medallion bust in the Poets' Corner of Westminster Abbey, beginning,

Olvarii Goldsmith,
Poetae, Physici, Historici

and ending,

Obiit Londini,
April IV, MDCCLXXIV.

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Editorial

THE NATURE AND ETIOLOGY OF HODGKIN'S DISEASE

Aside from the reported discovery of various organisms in the involved tissues in Hodgkin's disease, the implication that this condition is of infectious origin has been found in histological rather than clinical evidence. Neither geographical distribution, nor age and sex incidence points in any significant way to a parasitic etiology. Of epidemiological aspects there are none save the not infrequent appearance of Hodgkin's disease in more than one member of a family; but this occasional observation is far less impressive than the familial incidence of certain other diseases, such as the retinal neuroblastoma, for instance, in regard to the neoplastic nature of which there is no difference of opinion. Also, when the invariably fatal outcome is considered in connection with the non-vital character of the structures first giving clinical evidence of involvement, no support for a belief in an infectious origin can be found. With those infectious diseases which entail the highest mortality, at least an occasional victim survives.

From the histopathological standpoint, however, Hodgkin's disease presents features which strongly suggest an infectious granuloma. Such are the variety of the microscopical changes and particularly the simultaneous occurence of multiple cell types, lymphoblasts, fibroblasts, eosinophils, and various giant cells, all tending as the process advances to give way to a mature or hyaline fibrosis on the one hand, or to pass into caseation necrosis on the other. It was some years ago that the writer was warned by the distinguished director of a certain European pathological institute to be particularly careful in the postmortem examination of a case of Hodgkin's disease, because "young men are especially susceptible to the infection". The sincere solicitude of the advisor was appreciated, but without conviction as to the gravity of the danger. Yet it must be acknowledged that the complex histopathology of Hodgkin's disease does invite the assumption that this disease is a chronic infectious granuloma, a view which is still entertained by many competent pathologists.

The recent work of L'Esperance[1] has encouraged those committed to the parasitic etiology of Hodgkin's disease, especially since Ewing has given some measure of support to this view. L'Esperance believed that the tubercle bacilli which she obtained from a case of Pel-Ebstein disease were of the avian type. From these studies she deduced that the avian tubercle bacillus probably has an etiological relationship to Hodgkin's disease. Is this but another episode in sequence with the many assertions and suggestions which have

[1] L'Esperance, E. S.: Study of case of Hodgkin's disease in a child, Jr. Immunol., 1930, xviii, 127-132.

gone before? Tubercle bacilli of strains unspecified, diphtheroids, pleomorphic cocci, amebae, and monilia have each been given a rôle, playing an aggressive or a timid part depending upon the degree of caution possessed by their respective proponents. The very multiplicity of these claims raises doubt that there is a parasitic cause, while many who believe that Hodgkin's disease is infectious in nature are driven to the conclusion that the etiological agent has not yet been discovered.

Through an experimental and analytical investigation Medlar[2] has advanced well-considered and significant opinions in respect to the changes and responses of the hematopoietic and lymphoid tissues to infection with the avian tubercle bacillus, and in regard to the essential nature of Hodgkin's disease. He found that the histopathology induced by intravenous infection of normal and of vaccinated rabbits with virulent avian tubercle bacilli was not significantly different from that produced by other types of tubercle bacilli. The differences in gross and microscopic pathology caused by tubercle bacilli of the avian, bovine and human types are to be explained by differences in virulence, in susceptibility and in dosage, and are not specific for type of infecting organism. The important differences produced by the avian bacillus in vaccinated and non-vaccinated animals demonstrated this point. In normal rabbits infection with avian bacilli produced constant lesions in the bone marrow. Among these were discrete collections of mononuclear leucocytes, sometimes necrotic, with varying degrees of infiltration with neutrophils. The hematopoietic tissue of the marrow was always hyperplastic, with numerous mitotic figures and increased megakaryocytes. Coincident with these changes in the marrow, there was an increase in the circulating mononuclear leucocytes. The megakaryocyte seemingly plays an important rôle in acute avian tuberculosis in the rabbit.

These observations of Medlar bring to mind those occasional examples in man in which a blood picture simulating an atypical leukemia is produced by an overwhelming miliary tuberculosis. One case known to the writer was believed to be an unusual leukemia on the basis of the increased number and preponderance of young mononuclear cells in the circulating blood. At autopsy rupture of caseous bronchial nodes into a pulmonary artery was demonstrated; and the bone marrow showed countless miliary foci of necrosis and young tubercles.

In Medlar's animals which had been infected intravenously with virulent avian tubercle bacilli, there were no gross pathological lesions simulating Hodgkin's disease. Microscopical examination showed in the lungs, liver and spleen a few to many giant cells which were indistinguishable from the giant cells seen in Hodgkin's lesions. The bone marrow in these animals was markedly hyperplastic and showed a marked increase of megakaryocytes. These were found in the process of entering the circulation as well as within

[2] MEDLAR, E. M.: Avian tuberculosis in normal and vaccinated rabbits, Am. Jr. Path., 1931, vii, 475-489; The significance of lesions resembling Hodgkin's disease in tuberculosis, ibid., 491-497; An interpretation of the nature of Hodgkin's disease, ibid., 499-513.

the blood sinuses of the marrow. These findings led to the conclusion that the giant cells observed in the tissues were also megakaryocytes. These lesions, suggestive of Hodgkin's disease, were not found in animals, which, by reason of smaller dosage or partial protection through vaccination, were able to survive for several months or longer. Moreover, essentially the same lesions were produced in experimental animals inoculated with virulent bovine and human tubercle bacilli, when the course of the disease was rapid but not when death occurred after a longer interval. Thus it appears that the avian organism has no monopoly on the production of this type of reaction. The megakaryocytes in the acutely tuberculous animals Medlar found to be closely similar to the Sternberg giant cells of Hodgkin's disease. But the presence of megakaryocytes in the circulation and lodged as emboli in the capillaries of the lungs is not a condition peculiar to acute tuberculosis. It is not specific for any condition, but occurs in various toxic and infectious states.

Medlar never observed the pleomorphism of cells or the other cellular appearances of true Hodgkin's disease in his experimental animals, and concluded that not only is Hodgkin's disease not produced by any type of tubercle bacillus but that no infectious agent can be the etiological factor. On the contrary his investigations led him to the belief that Hodgkin's disease is a malignancy of the bone marrow for which the megakaryocyte is the type cell, and that the characteristic histopathology of Hodgkin's disease is explainable as a pleomorphic aggregation of cells which represent the developmental cycle of the magakaryocyte. The origin of lesions outside of the bone marrow he believed to be due to metastasis. The term "megakaryoblastoma" was suggested to designate true Hodgkin's disease.

The new element in Medlar's analysis is the designation of the megakaryocyte as the stem cell for the origin of Hodgkin's disease and the consequent localization of a primary focus in the bone marrow. It will not be easy to prove that the process by which the disease becomes generalized is one of metastasis and not simply the manifestation of a neoplastic system dyscrasia. May it not be true that cells potentially capable of giving rise to premegakaryocytes are to be found widely distributed in the reticulo-endothelial system outside of the bone marrow? The 'myeloid' reaction is seen in many situations in the body, such as the submucosa and subserosa of the bladder, for instance, where it appears to have arisen *de novo*. At any rate, these stimulating papers by Medlar give added support to the view that Hodgkin's disease is a neoplastic process genetically related to lymphoblastoma, myeloma, chloroma and the leukemias.

Abstracts

The Plantar Reflex, its Significance, the Methods of its Examination and the Causes of Some Diagnostic Errors. By THEODOR DOSUZKOV, M.D. (The Jr. of Nerv. and Ment. Dis., 1932, lxxv, 374-383.)

The plantar reflex should be examined with the patient in the dorsal position, with his extremities extended and with the feet resting on the heels. A blunt needle or a pin should be the instrument used and never an object with a wide end, such as the handle of the neurologic hammer. In making the examination the pin should be traced slowly along the internal and external edges of the foot-sole from the heel to the elevation above the metatarsophalangeal joint, but not on that elevation. The reactions that are to be observed are: (1) movement of the toes, (2) tension of the 'm. tensoris fasciae latae', (3) movement in the big joints (talocrural, knee and hip). The movement of the toes has been the most studied. Its normal display, plantar flexion and adduction, is present in from 88 per cent to 98 per cent of normal persons in various series studied. The modifications of this reflex can be both quantitative and qualitative. Of the qualitative modifications inversion is the most important, but of this 'Babinski's phenomenon' there exist several varieties. The complete form displays itself in the dorsal flexion of all five toes. A frequent form is that of dorsal flexion of the first toe and plantar flexion of the other four. This is the form frequently meant when the presence of Babinski's phenomenon is mentioned in case reports. Other forms are dorsal flexion of the first toe or of all toes, appearing upon irritation of the external side only of the sole of the foot, while irritation of the internal side produces the normal reflex; and inconstant inversion of the reflex, alternating with the normal form of plantar reflex or with its entire absence. All of these phenomena have the same significance. They practically always mean a lesion of the pyramidal system. Diagnostic errors dependent upon the plantar reflex fall into two main groups. One of these is derived from technical faults of which the most common are an incorrect position for the patient during the examination, the use of an unsuitable instrument (usually the handle of a neurologic hammer), and the examination of the reflex from the part of the sole of the foot below the toes (by which method the positive Babinski's phenomenon may be caused to appear in healthy persons). The other group depends upon incorrect appreciation of properly obtained facts. Here the chief cause of error lies in ignoring the 'physiological Babinski', 'peripheral Babinski', 'pseudo-Babinski', 'pseudo-Puusepp', and 'pseudopathological Babinski'.

"Bothriocephalus Anemia" — Diphyllobothrium Latum and Pernicious Anemia. By IVAR W. BIRKELAND, M.D. (Medicine, 1932, xi, 1-139.)

The fish tapeworm has been reported in more than 250 cases of infestation of human beings on the continent of North America. At least twenty-three cases have been reported in patients who have spent their entire lives in this part of the world. The frequency of infestation is increasing so that the fish tape-worm is now estimated to be the most common cestode in the North-Central States and Central Canada. In New York City, as well as in Chicago and Minneapolis, the numerical predominance of this parasite over the pork and beef tapeworms has been recognized. While a majority of those harboring the fish tapeworm suffer no ill effects therefrom, some show a variety of clinical manifestations without anemia, with symptoms referable to the central nervous system or to the alimentary tract. In nonanemic carriers there may be noted an altered blood picture which has been defined as an abortive form of Diphyllobothrium anemia. When

present, the fully manifest anemia runs true to type with but very few exceptions, and as a rule it is indistinguishable from cryptogenetic pernicious anemia, clinically, hematologically, and pathologically. Achlorhydria is present in about 84 per cent of cases of Diphyllobothrium anemia. When hydrochloric acid is present, the acidity is usually below the average level. The incidence of spinal cord changes in association with this type of anemia has not been thoroughly investigated. Numbness and tingling in the hands and feet are not uncommon complaints. Prior to the recognition of the etiologic significance of the tapeworm in relation to this anemia, the same grave prognosis prevailed as for cryptogenetic pernicious anemia until the introduction of treatment with liver. Systematic anthelmintic measures have greatly reduced the mortality, and the cure of the anemia thus obtained is remarkably permanent. Since in Finland only one of 5,000 to 10,000 carriers of this worm develops a definite anemia, it is obvious that the worm cannot be the sole factor involved in the production of the anemia. Peculiarities of the constitution—racial, familial, and individual—must have to do with the ultimate susceptibility which makes the development of this type of anemia possible. This means a specific predisposition for the development of anemia of the pernicious type.

The National Leper Home (United States Marine Hospital), Carville, La. Review of the More Important Activities during the Fiscal Year Ended June 30, 1931. By O. E. Denney, F.A.C.P., Surgeon, United States Public Health Service. (Public Health Reports, 1932, xlvii, 601-613.)

During the fiscal year ending June 30, 1931, the average daily population of The National Leper Home at Carville, La., was 322. Sixty-three new patients were admitted; 3 absconded, of whom one returned within one month at his own expense; 9 patients who had absconded in previous years returned for hospitalization, 5 of them paying their own expenses. Nineteen patients were paroled. Of the 337 patients in the hospital on June 30, 1931, 178 were taking chaulmoogra oil by mouth, the dosage varying from 5 to 125 drops three times a day. About one-third of the patients were taking chaulmoogra oil with benzocaine by intramuscular injection twice weekly, the average dose being 5 c.c. Of the 49 patients who had been taking the intramuscular treatment for two years, 33 were markedly improved, 14 were moderately improved, and 2 were slightly improved. Of 131 patients who had taken treatment for over 12 months, 66 showed marked improvement, 50 showed moderate improvement, 8 showed slight improvement, and 7 were unchanged. Of the two groups, 34 were bacterioscopically negative. Forty-eight patients were treated with the ethyl esters of hydnocarpus. Intramuscular injections of the esters in doses of 2 or 3 c.c. were given once a week and proved much less irritating than the esters of chaulmoogra oil. The beneficial results were about equal to those obtained with the ethyl esters of chaulmoogra oil. The sera of all new patients were examined by the Kolmer quantitative complement fixation method and Kahn precipitation test. Of the 110 examinations made by each method, 49 sera were negative by both Kolmer and Kahn methods; 24 were negative by Kolmer and positive by Kahn, 10 of which showed a 3 plus or higher reading by the Kahn method; and 6 were negative by Kahn and positive by Kolmer, all but 3 of which, however, showed a weakly positive reading by the Kolmer method.

The Present Status of BCG Vaccination. By S. A. Petroff, Ph.D. (The New Engl. Jr. of Med., 1932, ccvi, 436-439.)

No problem in tuberculosis, since the famous controversy on the entity of bovine and human tuberculosis some twenty-five years ago, has created such a feverish discussion as the prophylactic immunization against tuberculosis known as BCG vaccination. From study of three different cultures of BCG, obtained at different times and from three different sources, the last directly from Professor Calmette, Petroff came to the conclusion that BCG was an organism of low virulence, producing tuberculous changes which had the tendency to heal. But with each of the three cultures, a small number of ani-

mals which had been under observation for about eighteen months developed progressive tuberculosis. The organism isolated from the lesions of these animals, when inoculated into healthy guinea pigs produced a progressive disease which could be transferred in a series of animals. Dissociation phenomena may be appealed to to explain the instability of the organisms and the resulting variation in virulence. The differentiation of human and bovine tubercle bacilli by animal inoculation is at present inadequate. Among the cultures obtained from human material, a large number canpot be classified as either human or bovine. As to the Lübeck disaster, Petroff does not believe that the vaccine used for the babies was contaminated with human type tubercle bacilli, but that reversion of the virulence had taken place. Petroff is strongly opposed to the use of a living virus as a vaccine against tuberculosis. An organism which is now nonvirulent may regain its virulence after passing through a suitable environment and in time may become a menace to the person who has been vaccinated.

Über Ulkuszunge [*Ulcer Tongue*]. By PROF. DR. K. GLAESSNER. (Arch. f. Verd.-Krankh., 1932, li, 68-73.)

In patients with gastric or duodenal ulcer there is frequently found a characteristic change in the tongue consisting of solitary or multiple epithelial defects. These occur chiefly in the posterior segment of the tongue, either in the mid-line or anterior to the circumvallate papillae. They are frequently symmetrical but may be unilateral and exhibit a defect which lays bare the corium. They are round or oval, frequently elongated, are entirely superficial, non-painful and give the impression of superficial ulcers. In size they range from 2 to 8 m.m. in diameter. Glaessner has seen these lesions in more than 50 cases. Their presence speaks for peptic ulcer, but their absence must not be taken as evidence against an ulcer diagnosis. Once present, the tongue lesions appear to remain as long as the gastric ulcer persists. With its healing they disappear. The author believes this to be a hitherto undescribed form of glossitis characteristic for peptic ulcer.

Reviews

A Diabetic's Own Cook Book. By STELLA H. LYONS; with a foreword by LOGAN CLENDENING, M.D., F.A.C.P., xii + 94 pages. Alfred A. Knopf, New York City, 1932. Price, $2.00.

Mrs. Lyons is a good cook—and also a diabetic. How often, when faced with the common "hospital" list of foods useful for this ailment, has the physician been told "I'd rather die than diet!" Certainly, in her little volume "A Diabetic's Own Cook-Book", Mrs. Lyons has taken the "die" out of "diet". And —blessed relief to the diabetic,—she has done it without entangling him in a mass of weighing-scales, measuring glasses and logarithm-like tables of figures. In fact, the only evidence of these bug-a-boos lies on the title page set up by the publisher. After a common-sense layman's talk to the layman, dealing with the principles of feeding necessary to diabetics, Mrs. Lyons plunges at once into her main task; food and how to cook and serve it. It's good food, too, food which any *non*-diabetic could and would enjoy. Moreover, the recipes, practically, are criticism-proof from the technical viewpoint. These recipes should prove most helpful not only to diabetics but also to dieteticians in institutions who have "worn out" their stock meal-lists and to physicians who wish to put "life" into the sober lists of "allowed" foods as set forth in standard books on dietetics. Not in the least in value is the wholesome, "good housewife" optimism which pervades Mrs. Lyons' brochure. Steffanson startled the professional North Pole chaser with his book entitled "The Friendly Arctic"; Mrs. Lyons similarly has removed a host of horrors by her courage in being "friendly" toward diabetes and its demands of "eating to live".

FRANK SMITHIES, M.D., M.A.C.P.

Italian Medicine. By ARTURO CASTIGLIONI, M.D., Professor of the History of Medi-

cine, Royal University of Padua, Italy. Translated by E. B. KRUMBHAAR, M.D., Professor of Pathology, University of Pennsylvania. xi + 134 pages. 11 illustrations. Paul B. Hoeber, Inc., New York City, 1932. Price, $1.50.

Italian Medicine is the sixth member of the Clio Medica series. Like its predecessors it provides in readily portable form—in a coat pocket size, in fact—a readable survey of a limited field in medical history. It is intended to orient the reader in the special domain of the subject. The sponsors of the series are fortunate in securing an eminent Italian scholar of the History of Medicine as author. The translation is also excellent. It has a literary value of its own and is free from the idiom of the original. The reviewer questions the suitability of the subject for a Clio Medica volume. Would it not have been better to have subdivided the topic in order to permit fuller treatment? The author himself writes, "The history of Italian medicine is too vast and complex to be concentrated in a small volume. I have tried merely to outline its history in its high points from the time of the school of Salerno to the present day. It would not be possible even to name all the famous schools and illustrious physicians." The typography is good and the binding serviceable. In a modestly priced volume an excellent reference handbook to the more significant men and events in Italian Medicine is provided. If the subject proved too large for treatment in so small a compass, all the more does this book whet the appetite for a larger portion, and this is one of the aims of Clio Medica.

Female Sex Hormonology: A Review. By WILLIAM P. GRAVES, A.B., M.D., F.A.C.S., Professor of Gynecology at Harvard Medical School, Surgeon-in-Chief to the Free Hospital for Women and to the Parkway Hospital, Brookline, Massachusetts. 131 pages, 9 illustrations. W. B. Saunders Company, Philadelphia and London, 1931. Cloth, $3.00.

This little book is in truth an interesting review of female sex hormonology. The author first deals with the very earliest work which proved the ovary to be a gland of internal secretion. He briefly reviews the sex cycles in animals. After discussing the cycle in the ovary, he describes the uterine cycle and its correlation with that of the ovary. This relationship is clearly illustrated with diagrams. The author reminds the reader how closely the last phase of the endometrial change imitates an early decidual change, a fact of some importance. The animal experimental work is described which led to the isolation of the two ovarian hormones and the functions of these hormones, the finding of "folliculin" in various tissues of the female and even in the male and in plants. Later it was found that the corpus luteum also secretes a specific hormone, which prepares the uterus for the reception of the embryo. It has been proven that the secretion of the follicle and of the corpus luteum are antagonistic and are also synergistic. The author questions whether these two known hormones are simple or complex. The work leading to the development of the Ascheim-Zondek test, and the subsequent finding of at least two hormones of the anterior lobe of the hypophysis and their correlation with the ovarian hormones are fully presented. These investigations have led to new theories of menstruation, parturition and lactation. The author constantly emphasizes the rhythm of the sexual cycle in all its functions. The lack of success in organotherapy in the past he believes to be due largely to the use of extracts from the wrong organ. At the end of the book is a useful glossary and under the definition of "hormone" is a list of some of the proprietary hormone preparations, classified as to source. There is also an extensive bibliography. This book is stimulating and well worth reading.

Síndrome de Oclusion Coronaria [The Syndrome of Coronary Occlusion]. By ANTONIO BATTRO, Médico Agregado del Hospital Nacional de Clínicas, Médico Inspector del Dispensario Público Nacional Antituberculoso de Belgrano, Adscripto a la Cátedra de Clínica Médica. 214 pages, 111 figures. Librerio "El Arteneo", Buenos Aires, 1930.

This is an excellent monograph on occlusive disease of the coronary arterial system. The first 38 pages are given over to anatom-

ical considerations and are supplied with excellent illustrations, in part from Spalteholz and other sources, and in part original. The next section deals with the physiology of the coronary circulation, including the coronary vasomotor mechanism and the action of certain drugs. A brief discussion of etiologic factors is followed by a description of the clinical syndrome of myocardial infarction. In the remaining sections the following topics are presented: An experimental and clinical study of coronary occlusion by the electrocardiograph, the evolution of the syndrome, the pathological anatomy of coronary occlusion, the clinical forms of the syndrome, differential diagnosis, prognosis, and treatment. The bibliography contains 188 titles, and there is a table of contents in outline form.

Clinical Atlas of Blood Diseases. By A. PINEY, M.D., M.R.C.P., Director of Pathological Department, The Cancer Hospital, London; Consulting Pathologist, Chelmsford Hospital; and STANLEY WYARD, M.D., M.R.C.P., Physician, The Cancer Hospital, London, and Princess Beatrice Hospital. Second edition. xvi + 105 pages. 38 illustrations of which 34 are in color. P. Blakiston's Son and Company, Inc., Philadelphia, 1932. Price, $4.00 net.

This small book combines the functions of an hematological atlas and of a concise textbook upon the diseases of the blood. The necessity for a second edition within two years of the first is sufficient evidence that the work is supplying an actual need. The color plates, for the greater part, give the appearances of the various types of blood cells as stained by the Jenner-Giemsa method, at a magnification of 1,000 diameters. A brief, and therefore necessarily somewhat dogmatic, account of almost all hematological diseases is provided. The omission of any reference to ovalocytosis is noted, but sickle cell anemia has both a color plate and a discussion. A glossary of hematological terms, brief expositions of the Arneth and Schilling indices, 'family trees' of the various blood cells, and an all too brief appendix on the technic of blood examination are included. This book can be fully recommended for its purpose. The price is justified by the numerous figures in colors.

How's Your Blood Pressure? By CLARENCE L. ANDREWS, M.D., F.A.C.P., Attending Physician and Medical Chief at the Atlantic City Hospital. x + 225 pages. The Macmillan Company, New York City, 1931. Price, $2.50.

This little book is written for "the victims of blood pressure psychology who . . . . live in constant fear of some impending calamity which may never occur". Couched in simple language intended to elucidate the subject of blood pressure for the laity, free use is made of homely similes to illustrate the physiology and anatomy of the circulation. The author takes up first in a general way the need for a circulatory system, then treats of some of the factors concerned with the maintenance of the blood pressure in health and disease. The general facts concerning blood pressure and its variations are accurately stated and no exception can properly be taken to the author's advice for the maintenance of a sound circulation. That faulty blood pressure is not a disease *per se*, is constantly kept before the reader. Perhaps, in an effort to state his thesis simply, the author has erred in the direction of excessive simplicity of style and in the presentation of facts already well known to intelligent laymen; but sound advice, sympathetically set forth, characterizes this thoroughly wholesome book.

Das Chlorophyll als Pharmakon [*The Pharmacology of Chlorophyl*]. By PROF. DR. EMIL BÜRGI. 84 pages, 28 graphs. 1932, George Thieme, Leipzig. Price, M. 6.40.

In this well-printed monograph various pharmacologic aspects of chlorophyl are considered in detail. Such are its part in the synthesis of hemoglobin and development of erythrocytes; its further effects upon the blood picture; its tonic effects upon the organism as a whole and upon certain organs and tissues, and its dosage and therapeutic availability. Two and one-half pages of bibliographic references to chlorophyl are appended.

ADDITIONAL BOOKS RECEIVED

Proceedings of the Twenty-Fifth Annual Convention of The Association of Life Insurance Presidents. (GEORGE T. WIGHT,

Secretary, 165 Broadway, New York City.) 278 pages. 1931.

Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year, 1931. vii + 354 pages. United States Government Printing Office, Washington, D. C. 1931. Price 85 cents, bound in cloth.

Origin of Cancer. The Specific Cancer Cell of Carcinoma, Contrasted with the Normal Matrix Embryonal Cellule of Primal Ovum Days, to 8th Week; [etc.]. By FRANK A. STAHL, M.D.; Chicago, Ill. 96 pages, 1932. Privately printed.

Prohibiting Minds and the Present Social and Economic Crisis. By STEWART PATON, M.D., Lecturer on Psychiatry, Johns Hopkins University, Baltimore. xii + 198 pages. Paul B. Hoeber, Inc., New York City, 1932. Price, $2.00. (See quotation on p. 1403.)

Experimental Studies of Dengue. By JAMES STEVENS SIMMONS, Major, Medical Corps, United States Army; JOE H. ST. JOHN, Major, Medical Corps, United States Army; and FRANCOIS H. K. REYNOLDS, Captain, Veterinary Corps, United States Army. viii + 489 pages, 3 plates and 159 text figures. Monograph 29 of the Bureau of Science, The Government of the Philippine Islands. Bureau of Printing, Manila, 1931.

Semiología de la Onda T del Electrocardiograma y su Interpretación Clínica. [Semiology of the T Wave of the Electrocardiogram and its Clinical Interpretation.] By ANTONIO BATTRO. 121 pages, 66 illustrations. Sebastián de Amorrortu; Ayacucho, 774; Buenos Aires, Argentina.

The Cause of Cancer. By W. E. GYE, M.D., and W. J. PURDY, M.B.; Members of the Scientific Staff of the National Institute for Medical Research, London. xiv + 515 pages, 105 illustrations. Cassell and Company, Ltd., London, Toronto, Melbourne, Sydney, 1931. Price, 30 shillings net.

College News Notes

Acknowledgement is made of the receipt of gifts to the College Library of publications by members, as follows:

Dr. Edward E. Cornwall (Fellow), Brooklyn, N. Y.—1 reprint;

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;

Dr. Robert A. Knox (Fellow), Washington, Pa.—1 reprint;

Dr. William Gerry Morgan (Fellow), Washington, D. C.—1 reprint;

Dr. Frank Garm Norbury (Fellow), Jacksonville, Ill.—1 reprint;

Dr. Lea A. Riely (Fellow), Oklahoma City, Okla.—1 reprint;

Dr. Karl Rothschild (Associate), New Brunswick, N. Y.—1 reprint.

Dr. Lea A. Riely (Fellow), Oklahoma City, Okla., addressed the Fourteenth Quarterly Session of the Southern Oklahoma Medical Association, March 8, 1932, on "Diseases of the Gall Bladder".

The following Fellows of the College presented papers at an afternoon symposium sponsored by the Henry Ford Hospital, Detroit, Mich., on January 29, 1932:

Dr. Frank R. Menagh, Detroit,—"Food Hypersensitiveness and Hypothyroidism as Etiological Factors in the Treatment of Chronic Eczema".

Dr. John G. Mateer, Detroit,—"Dietary, Foreign Protein, and Nervous Factors in the Treatment of Chronic Irritable Colon".

Dr. Frank J. Sladen, Detroit,—"Chronic Undulant Fever—A Food-borne Disease Problem", and later, in conjunction with another physician, Dr. Sladen held a "Clinical-Pathological Conference".

Dr. Erwin D. Funk (Fellow), Wyomissing, Pa., has been in Berlin, Germany, the last three months studying the relation of hospitals to communities, and hospital management under a grant from the Oberlaender

Trust and Carl Schurz Foundation. Later he will go to Vienna.

Dr. Elliott P. Joslin (Fellow), Boston, Mass., was awarded the Kober Medal by the Association of American Physicians, at a meeting of the Association in Atlantic City on May 4. The medal was awarded to Dr. Joslin because "for many years, he has been one of the world's leading authorities on diabetes mellitus. He has carried on important researches in this field. He has simplified and standardized treatment. He has been a great educator in the management of diabetes. He has trained doctor, nurse and patient in the use of his methods both individually and by group instruction. His textbook on diabetes, which has gone through four editions is a mainstay of both physician and medical student. His small manual is the bible of the diabetic patient. It is believed that his life work represents a type of sustained and scholarly performance for which Dr. Kober would have been glad to see his prize awarded."

Dr. Leonard G. Rowntree (Fellow), Rochester, Minn., has been appointed Director of the Philadelphia Institute for Medical Research, which will open its doors next fall at the Philadelphia General Hospital, according to a statement issued recently by Dr. Judson Daland (Fellow), Philadelphia, President of the Institute and one of its founders in 1922. Opening of the Institute will give Philadelphia, according to Dr. Daland and his colleagues, a research organization with few rivals the world over. In addition to its own research work, the new Institute will hold itself ready to cooperate in medical research by collaboration or affiliation with any or all medical and allied institutions desirous of establishing such relationship. It will ocupy a somewhat analogous position to that held by the Thorndike Institute of Boston. Dr. Rowntree, the new Director, was graduated in medicine at the University of Western Ontario in 1905. Since that time he has held many posts of importance among which are the following: associate professor of medicine at Johns Hopkins University School of Medicine; chief of the department of medicine of the University of Minnesota; member of the Air Service Medical Staff in France during the World War; senior medical consultant and director of Clinical Investigation of the Mayo Clinic.

The following Fellows of the College appear on the Medical Advisory Board of the Institute: Dr. S. Solis-Cohen, Dr. Joseph C. Doane, Dr. D. J. McCarthy, and Dr. Jefferson A. Clark.

Dr. E. J. G. Beardsley (Fellow), Philadelphia, addressed the Woman's Auxiliary of the Burlington County Medical Society at the Community House, Moorestown, N. J., on Monday, March 21. His subject was "Never Changing Truths Concerning Medicine and Life".

Dr. Ralph deBallard Clarke (Fellow), Meriden, Conn., took part in a symposium on collapse therapy at the Danbury (Conn.) Hospital on February 9, 1932. At this time he addressed members of the Danbury Medical Society and physicians from surrounding towns on the subject "Phrenicectomy and Artificial Pneumothorax in Tuberculosis of Children", illustrating his talk with X-ray films of cases under compression-therapy among children at Undercliff, the Connecticut State Childhood Tuberculosis Sanatorium at Meriden, Conn.

Dr. Roland N. Klemmer (Fellow), Lancaster, Pa., was elected Medical Director of the Lancaster County Hospital, Lancaster, Pa., at a recent meeting of the newly organized Staff.

Dr. Albert E. Russell (Fellow), Washington, D. C., was detailed by the Public Health Service to give an address on "Silicosis and Tuberculosis" at a joint meeting of the Trudeau Club and the St. Louis, Mo., Medical Society on April 5, 1932.

Dr. Lewis J. Moorman (Fellow), Oklahoma City, is President of the Southern Medical Association.

Dr. Charles Hartwell Cocke (Fellow), Asheville, N. C., Governor for North Carolina, is Second Vice-President of the same body.